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STUDIES ON MENISCUS SURGERY WITH FOCUS ON PRESERVATION AND MENISCUS FUNCTION

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STUDIES ON MENISCUS SURGERY WITH FOCUS ON PRESERVATION AND MENISCUS FUNCTION

THESIS FOR DOCTORAL DEGREE (Ph.D.)

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Solemnly dedicated to my beloved and proud wife

ABSTRACT

The aim of this thesis was to investigate the effect of surgical preservation and restoration of the meniscus on knee function and outcomes.

In *Study I*, 4497 patients with primary hamstring ACLR were evaluated regarding knee laxity preoperatively and at 6-months follow-up using KT-1000. The primary aim was to evaluate the ATT depending on type of treatment of meniscus injuries in conjunction to primary ACLR. A significant reduction in laxity was found for all patients. Medial meniscus resection resulted in significantly increased laxity compared to isolated ACLR. Medial meniscus repair resulted in laxity comparable to isolated ACLR.

In *Study II*, all ACLRs from the SNKLR were evaluated. The primary aim was to compare KOOS and EQ-5D at 2-year follow-up after isolated ACLR to ACLR with associated meniscus injury treated with either repair or resection in the Swedish National Knee Ligament Register. Meniscus resection resulted in worse outcome, whereas meniscus repair resulted in comparable outcome to isolated ACLR.

In *Study III*, 918 meniscus repairs were analysed. The primary aim was to assess failure within three years. Repair with arrows and medial repairs resulted in significantly more failures than repair with anchors and lateral repairs. Concomitant ACLR resulted in less failure of meniscus repair than isolated meniscus repairs.

In *Study IV*, 316 consecutive meniscus repairs were followed up with radiology, KOOS and Lysholm. The primary aim was to determine the effect of meniscus repair on OA and secondly its effect on subjective knee function. Failed meniscus repair resulted in significantly higher risk for OA and worse patient reported outcome.

In *Study V*, seven cases of meniscus transplantation using the semitendinosus tendon are described. The surgical technique is described in detail. Four patients had completed the 12-month follow-up and report significantly improved outcome in IKDC Global Score, KOOS pain subscale and Lysholm.

In conclusion, meniscus repair result in less OA and better subjective knee function than meniscus resection. Medial meniscus repair provides less knee laxity than meniscus resection. Failure after meniscus repair are more common for medial and isolated repairs. In cases of post meniscectomy symptoms, the semitendinosus tendon could possibly function as a meniscus transplant with improved knee function for the patients.

LIST OF SCIENTIFIC PAPERS

This thesis is based on the following studies. Referral in the text will be by their roman numbers.

I. **Medial Meniscus Resection Increases and Medial Meniscus Repair Preserves Anterior Knee Laxity: A Cohort Study of 4497 Patients with Primary Anterior Cruciate Ligament Reconstruction.** R Cristiani, E Rönnblad, B Engström, M Forssblad, A Stålman.
Am J Sports Med. 2018 Feb;46(2):357-362.

II. **Meniscus Repair With Simultaneous ACL Reconstruction Demonstrated Similar Clinical Outcomes as Isolated ACL Repair: a Result Not Seen With Meniscus Resection.** M Phillips, E Rönnblad, L Lopez-Rengstig, E Svantesson, A Stålman, K Eriksson, O R Ayeni, K Samuelsson.
Knee Surg Sports Traumatol Arthrosc. 2018 Aug;26(8):2270-2277

III. **Predictive Factors for Failure of Meniscal Repair: A Retrospective Dual-Center Analysis of 918 Consecutive Cases.** E Rönnblad, B Barenius, B Engström, K Eriksson.
Orthop J Sports Med. 2020 Mar 27;8(3):2325967120905529

IV. **Failed Meniscal Repair Increases the Risk for Osteoarhritis and Poor Knee Function at an Average of Nine Years Follow-up.** E Rönnblad, B Barenius, A Stålman, K Eriksson.
Submitted.

V. **Autologous Semitendinosus Tendon as Meniscal Transplant – a Pilot Study.** E Rönnblad, P Rotzius, K Eriksson.
Manuscript.

CONTENTS

LIST OF ABBREVIATIONS

ACL	Anterior cruciate ligament
ACLR	Anterior cruciate ligament reconstruction
AP	Anteroposterior
ATT	Anterior tibial translation
BMI	Body mass index
BPTB	Bone patella tendon bone graft
CI	Confidence interval
CL	Contralateral
HT	Hamstring tendon
IKDC	International Knee Documentation Committee
KOOS	Knee Osteoarthritis Outcome Score
ADL	Activities of daily life, subscale in KOOS
Sport/Rec	Function in sport and recreation, subscale in KOOS
Pain	Symptoms of pain, subscale in KOOS
Symptoms	Other symptoms, subscale in KOOS
QoL	Knee-related quality of life, subscale in KOOS
LCL	Lateral collateral ligament
MCL	Medial collateral ligament
MRI	Magnetic resonance imaging
N	Newton
OA	Osteoarthritis
PCL	Posterior cruciate ligament
PROM	Patient Recorded Outcome Measure
QT	Quadriceps tendon
RCT	Randomized controlled trial
ROM	Range of motion
SD	Standard deviation
SNKLR	Swedish national knee ligament register

DEFINITIONS

ACL reconstruction	Surgical reconstruction of the ACL using a graft
Allograft	Graft using the tissue from a donor of the same species
Autograft	Graft with tissue taken from one part to another in the same individual
Closed kinetic chain exercises	A physical exercise where the limb is fixed.
Confidence interval	The probability that a sample (population) parameter will fall within a set of values for a proportion of times. Measures the degree of certainty or uncertainty in a sampling method. Probability limit is typically 95% or 99%.
Contralateral	Belonging to or occurring on the opposite side of the body
Ipsilateral	Belonging to or occurring on the same side of the body
Instability	Subjective perception of unreliability of a joint due to increased looseness compared to normal
Laxity	An objective finding of looseness of the joint
Meta-analysis	A systematic review that uses quantitative methods to analyze pooled data
Null hypothesis	A hypothesis used in statistics that proposes that there is no difference between certain characteristics of a population
P value	The probability, under the null-hypothesis, of obtaining a result equal to or more extreme than what was actually observed
Power	The power is the probability of detecting an effect, given the effect is there, i.e. avoiding a Type II error.

Prospective	A study form looking forward in time or gathering data for future analysis
Regression analysis	Statistical method for assessing the degree of correlation of a dependent variable adjusted to one or several independent variable(s)
Retrospective	A study form looking backward in time or dealing with past events
Revision surgery	Replacement of a failed previous ACL reconstruction
Sensitivity	Percentage of patients with an outcome who are classified as having positive results and are truly positive
Specificity	Percentage of patients without an outcome who are classified as having negative results and are truly negative
Systematic review	A review of a clearly formulated question that uses systematic and explicit methods to identify, select and critically appraise relevant research. The data from the included studies are then collected and analyzed
Type I error	Incorrect rejection of a true null hypothesis (“false positive”), an overestimation of the relationship
Type II error	Failure to reject a false null hypothesis (“false negative”), often due to lack of power, or an underestimation of the relationship

1 THE MENISCUS

1.1 ANATOMY

The menisci are two fibrocartilaginous semilunar shaped structures in the knee, positioned between the joint surface of the lateral and medial part of the convex femur and the flat tibia. From a cross section view the menisci are wedge-shaped. The thicker peripheral base is attached to the capsule of the joint and the thin apex with a free edge is centrally placed [1]. The femoral surface of the menisci is concave and the tibial surface is flat. The menisci also have central attachments through posterior and anterior roots. The medial meniscus has additional attachment to the profound part of the medial collateral ligament [1] and the meniscotibial ligament which spreads like a curtain from the deep part of the undersurface of the meniscus down to the vertical aspect of the tibia [2 3]. The lateral meniscus does not attach to the lateral collateral ligament, is not as tightly attached to the capsule and also has a non-attached area adjacent to the popliteal tendon [2]. As a consequence the lateral meniscus is less rigid than the medial [4]. During flexion both menisci translates posteriorly, the lateral to a greater extent than the medial [5 6]. The lateral meniscus posterior horn also attaches to the medial femoral condyle by the Humphrey ligament going anteriorly to the PCL and the Wrisberg ligament passing posterior to the PCL [7]. The medial meniscus is crescent shaped and cover up to 60% of the articular tibial plateau. The lateral meniscus has a more circular shape and covers around 80% of the lateral tibial surface [8]. The medial meniscus is bigger than the lateral with an average circumferential length of circa 100 mm, in comparison to 92 mm for the lateral meniscus [9].

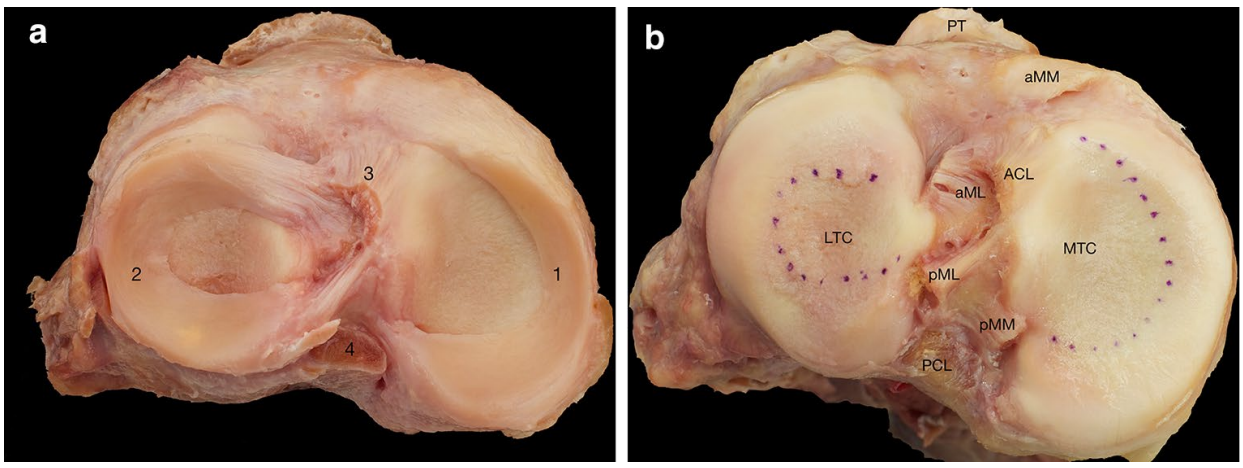

Figure 1. a Anatomical dissection showing the menisci. 1 medial meniscus; 2 lateral meniscus; 3 ACL; 4 PCL. **b** The articular surface of the proximal tibia. ACL, anterior cruciate ligament; aML, anterior root of lateral meniscus; aMM, anterior root of medial meniscus; LTC, lateral tibial condyle; MTC, medial tibial condyle; PCL, posterior cruciate ligament; pML, posterior root of lateral meniscus; pMM, posterior root of medial meniscus. (Reprinted with permission from Springer. Smigielski et al. [10])

The meniscal matrix components are about 65 % water, 22 % collagen and proteoglycans [11]. As opposed to cartilage of the joint, which is predominantly made up of collagen type II, roughly 90% of the meniscus dry weight is collagen type I. The main part of the collagen type I is found in the peripheral part of the meniscus and is produced by oval fibroblast-like cells. The central part of the meniscus on the other hand has round, small chondrocyte-like cells that produce collagen type II. On the surface of the meniscus there are flat progenitor cells that might have a regenerative function [12 13].

The collagen fibers are tightly woven, predominantly in a circumferential pattern. Radial fibers perforate and mesh the longitudinal ones, and additional superficial randomly oriented fibers. The network enables resistance to tension and shear forces.

The extracellular matrix of the meniscus comprises 70% water. The water binds to negatively charged hydrophilic proteins called proteoglycans. This contributes to the elastic properties and the ability to absorb compression. The rest of the meniscus is made up of proteins such as Elastin and Fibronectin [11].

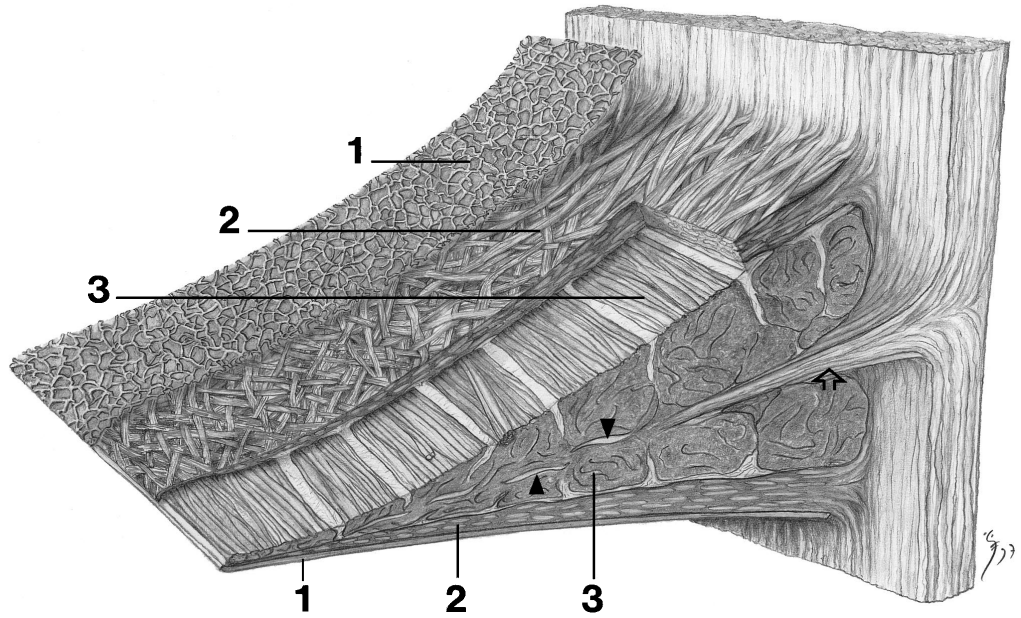

Figure 2. Cross section of the meniscus. 1: Superficial network by a meshwork of thin fibrils. 2: Lamellar layer of lamellae of collagen fibrils. 3: Central main layer with circular collagen fibrils. Arrow: Tissue from the capsule penetrating the circular bundles. (Reprinted with permission from Springer. Petersen et al [14])

1.2 NUTRITION AND INNERVATION

The meniscus is well vascularized during the prenatal period but decreases with time. The blood supplies from branches from the lateral, middle and medial genicular arteries. It is possible to divide the meniscus into three zones based on vascularization; the peripheral third, well vascularized called the red zone; the central third, avascular and receives nutrients through diffusion from the synovial fluid called the white zone; and the third in between,

partly vascularized thus called the red-white zone [15]. Prenatally the meniscus contains a high density of cells but gradually the content of collagen increases [15 16].

As the meniscus has better blood supply more peripherally (i.e. the red-red zone) there have been theories that more peripheral repairs would have better healing potential, which has also been indicated in some reports [17 18].

The outer third of the meniscus is innervated by the posterior articular nerve, a branch from the tibial nerve penetrating the capsule and following the vessels. The horns of the meniscus are mostly innervated and also contain mechanoreceptors that contribute to proprioception. The inner two thirds of the meniscus do not have any innervation [19 20].

1.3 FUNCTION

The meniscus is biomechanically important as its collagen-proteoglycan matrix enables it to transmit load and absorb shock forces in the knee joint [21-24]. At full extension of the knee joint, up to 50% of the strain distribution of the medial compartment is absorbed by the medial meniscus and up to 70% in the lateral compartment by the lateral meniscus [21 25]. The meniscus increases the weight bearing area as it forms a socket for the femoral condyle on the otherwise flat tibial surface [25 26]. As a result, the meniscus also contributes to the anteroposterior stability (medial meniscus) and rotational stability (lateral meniscus). The root attachment enables the meniscus to withstand the radial force applied when weight bearing as a counteracting tension load (hoop stress) is generated throughout the circumferential fibers. The wedge shape of the meniscus horns prevents the femoral condyle from posterior rolling during flexion and anterior translation of the tibia [8 27]. The meniscus is also suggested to contribute to better lubrication of the knee joint [28-31].

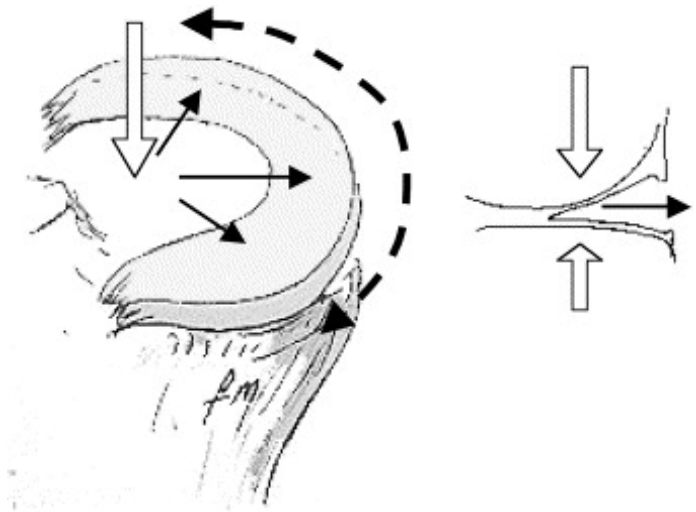

Figure 3. The axial load (white arrow) results in a radial force (black arrows) which is taken up as a circumferential force, hoop stress, in the meniscus (dashed arrow). (Reprinted with permission from Elsevier. Boyd et al. [32])

2 MENISCUS INJURIES

2.1 PREVALENCE AND CLASSIFICATION

The incidence of meniscus injuries is 6-12/10'000 persons/year in Sweden [33]. Meniscus injuries can be divided into degenerative or traumatic. A traumatic tear typically occurs when the meniscal tissue is normal, but the applied force exceeds the tissues resilience and causes its integrity to disrupt. This excessive force is often related to pivoting sports during twisting maneuvers, usually with the knee in flexion on weight bearing leg [34].

Not seldom the menisci are injured concomitantly to ligament injuries. In more than 40% of primary anterior cruciate ligament (ACL) reconstructions an associated meniscus injury has been reported [35-40], 60% for tears on the medial meniscus and 30% for lateral meniscal tears [1].

A common classification is based on the orientation of the tear. Traumatic tears are often longitudinal, vertical and run parallel to the circumferential fibers [41]. A complete longitudinal, vertical tear can give the so-called bucket-handle tear type. Sometimes the tear can be of radial orientation and run perpendicular to the circumferential fibers. Radial tears disrupt the circumferential fibers with a reduced resistance against circumferential stress, or so-called hoop-stress. Repair of radial tears is considered more challenging [42].

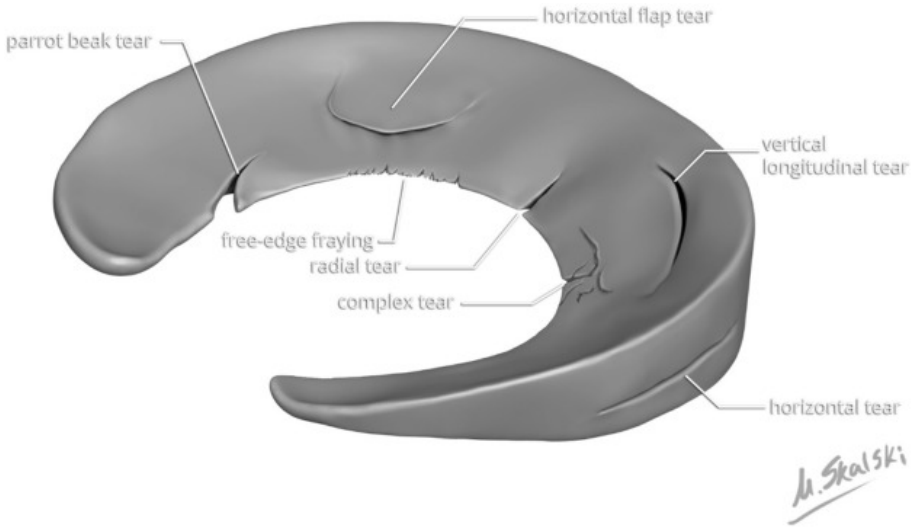

Figure 4. Illustration of different types of tears. (Reprinted with permission from Elsevier. Patel et al. [43])

Two other types of injuries are the ramp lesions and the root tears. The ramp lesion is a peripheral detachment of the posterior horn, typically seen in conjunction to ACL injuries [44]. Diagnosing the injury typically requires exploration in the posteromedial compartment why there might be an underestimation of the prevalence. The root tear involves an avulsion of the meniscus root attachment, disrupting the integrity of the circumferential fibers and resulting in a protrusion of the meniscus and thus loss of function [45].

2.2 MENISCUS REPAIR

The first documented surgical procedure on a meniscus was actually a meniscal repair, and was performed as early as 1883 by Sir Thomas Annandale [46]. One of the introducers of arthroscopic surgery was the Japanese surgeon Masaki Watanabe in 1962. In 1968 Robert Jackson introduced arthroscopic meniscus surgery in the USA [47]. In Sweden, Ejnar Eriksson and Jan Gillquist were early pioneers [48]. The advantages of arthroscopic surgery were several; less invasive, the possibility to perform outpatient surgeries, shorter rehabilitation time, lower complication rate and better visual overview [49 50]. With the increasing understanding of the meniscus function and improved surgical techniques, attention has shifted from resection towards meniscus repair over the past decades [51-53].

2.2.1 REPAIR TECHNIQUES

The aim of a meniscus repair is to restore the biomechanical properties of the meniscus. Different repair methods can be applied depending on the type of tear. Almost all meniscus repairs are today performed by arthroscopic technique. Only in the most peripheral and posterior tears of the medial meniscus, possibly combined with a tight compartment, or in conjunction to meniscus ganglions, the open technique might be useful.
When placing the meniscus suture, vertical configuration of the mattress has been shown to be the strongest in biomechanical studies [54-56]. Vertical sutures keep the circumferentially oriented fibers in the meniscus intact. As there is sometimes not enough room between the two condyles a vertical orientation is not always possible why the sutures need to be placed in an oblique or horizontal configuration.

2.2.1.1 Inside-out

The inside-out technique was the first arthroscopic repair method and is still considered gold standard by many. Via a cannula the sutures are passed from inside the knee, through the joint capsule where they can be tied under visual overview. Neurovascular structures need to be carefully protected with retractors when suturing the posterior horn. The method is still relatively widely used, but nowadays mainly for mid-body tears. With good overview, the sutures can be carefully placed in the desired fashion, possibly explaining the excellent pull-out strengths. Excellent long- and short-term results have been reported [57 58], especially for repairs of the lateral meniscus [17].

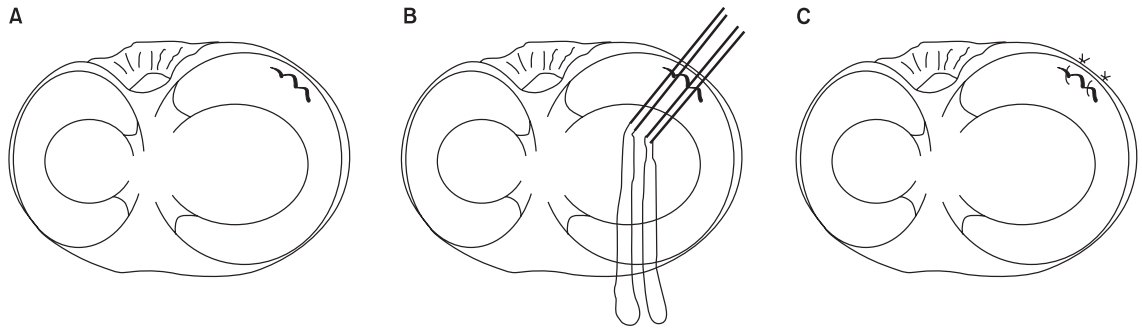

Figure 5. Inside-out repair. A: longitudinal tear. B: long needles with sutures introduced through cannulas. C: vertical sutures closing the tear. (Reprinted with permission from Knee Surg Relat Res. Yoon et al.[59])

2.2.1.2 Outside-in

As concern grew regarding the risk for neurovascular injuries with the inside-out technique, the outside-in technique was developed in the eighties [60]. Sutures are placed via needles or cannulas from the outside, through the meniscus and tied under visual overview. The method is most suitable for tears in the anterior and mid third of the meniscus [61].

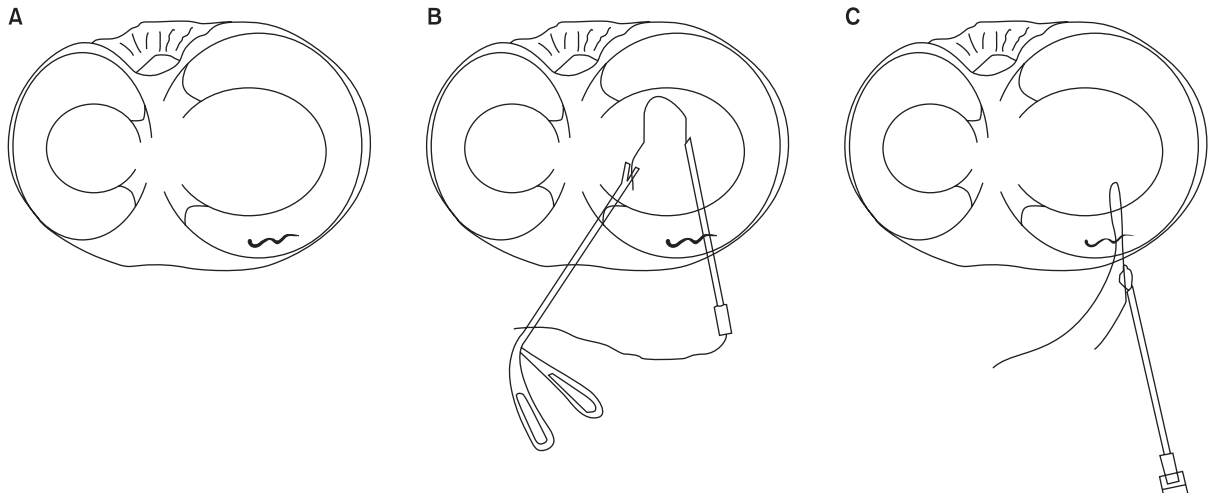

Figure 6. Outside-in repair. A: longitudinal tear. B: suture passed through needle. C: suture pulled out using wire-looped retriever. (Reprinted with permission from Knee Surg Relat Res. Yoon et al.[59])

2.2.1.3 All-inside

The all-inside techniques were developed as additional skin incisions were required for the inside-out and outside-in techniques, in addition to the risk of damaging neurovascular structures. The first generation of all-inside devices included rigid bio-absorbable arrows (Figure 5) or screws [62]. The rigid structure did however pose a risk for articular cartilage damage [63-67] and lower pullout strength combined with reports of less favorable outcome [63 68 69] led to the development of the second generation of all-inside sutures with anchors. The suture is fixed to the anchor which is deployed behind the capsule. A second anchor is then deployed and the suture connecting the two anchors is tightened creating a mattress suture. The first versions had anchors made of plastic, but there are today alternatives with knot-anchors. With a rapid transformation over the past years, the devices are now user-friendly and provide safe-insertion and reliable fixation. Even though there are reports of 88% success-rate at one-year follow-up for the Biofix arrows [70], the all-inside sutures with anchors are reported to be superior [64 71]. In a biomechanical study all-inside devices have been found to have equal load-to failure properties as inside-out sutures [72].

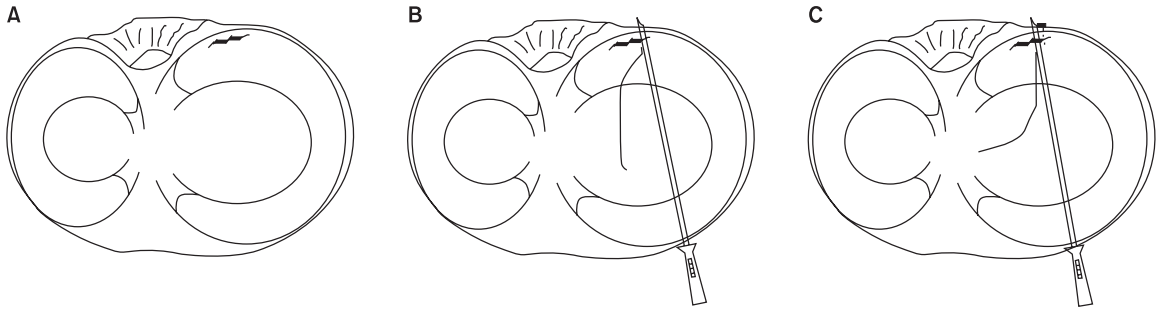

Figure 7. All-inside repair. A: longitudinal tear. B: suture device passed through tear site. C: deployment of first anchor. (Reprinted with permission from Knee Surg Relat Res. Yoon et al.[59])

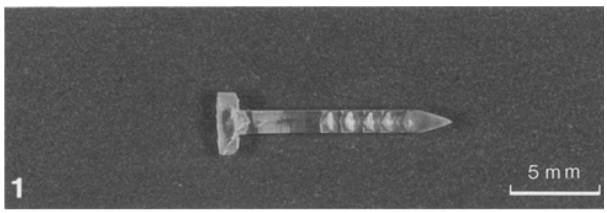

Figure 8. Bioabsorbable arrow.
(Reprinted with permission from Springer.
Albrecht-Olsen et al.[62])

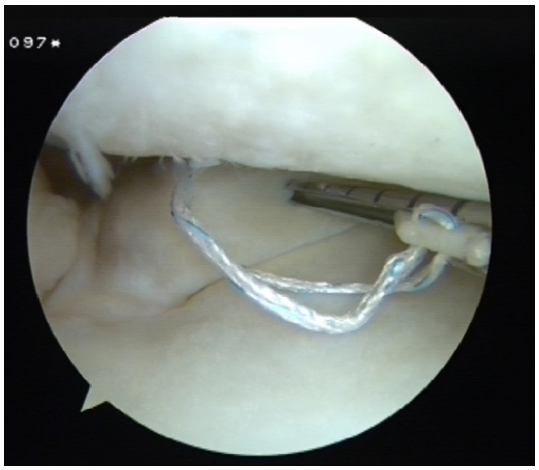

Figure 9. All-inside suture.

3 DIAGNOSIS

3.1 RADIOGRAPHY

Weight bearing plain radiography is considered "gold standard" for diagnosing OA in the knee joint. Radiographs can be taken in AP projection or the Rosenberg view where the image is taken posteroanteriorly at 45 degrees of knee flexion. Several systems for grading and interpreting the radiographic images exist. The Kellgren-Lawrence (KL) is the most adopted grading system for OA [73 74]. The standard cutoff for radiographic definition of OA is KL ≥ 2. The Fairbank classification was introduced to evaluate progression of OA [75]. Ahlbäck's classification was published in 1980 and is commonly used [76]. The grading for the different classification systems are presented in Table 1. Wright et al [77] presented moderate to good interobserver reliability for different classification systems and medium correlation to arthroscopic grading of the cartilage.

In *Study IV*, radiological examination was conducted using weightbearing Rosenberg view [78], and assessed according to the Kellgren-Lawrence (KL) classification [73] by the senior authors (K.E. and B.B.). In situations of uncertainty or when the senior authors disagreed on classification a radiologist was consulted. OA was classified as KL ≥ 2 (i.e. cartilage reduction ≤ 50% and/or significant osteophytes).

TABLE 1
Grading Scales for OA Classification

Scale	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Kellgren-Lawrence	No JSN or reactive changes	Doubtful JSN, possible osteophytic lipping	Definite osteophytes, possible JSN	Moderate osteophytes, definite JSN, some sclerosis, possible bone-end deformity	Large osteophytes, marked JSN, severe sclerosis, definite bone-end deformity
Fairbank	Normal	Squaring of tibial margin	Flattening of femoral condyle, squaring and sclerosis of tibial margin	JSN, hypertrophic changes, or both	All of the characteristics at left to a more severe degree
Ahlbäck	Normal	JSN <3mm or 50% of outer compartment, with or without subchondral sclerosis	Obliteration of joint space	Bone defect/loss <5 mm	Bone defect and/or loss 5-10 mm

Note: JSN, joint space narrowing.

3.2 MAGNETIC RESONANCE IMAGING (MRI)

For diagnosis and evaluation purposes of soft tissues in and around the knee joint, the MRI is regarded a superior tool. All soft tissue structures such as the meniscus, cartilage, ligament and synovia can be visualized and presented in a three-dimensional view in high resolution. For detecting meniscus injuries, the MRI is reported to have a sensitivity and specificity around 90% [79]. Makdissi et al. [80] did however present cases where lateral bucket-handle tears were not seen on the MRI, indicating lower sensitivity for lateral meniscus injuries.
An understanding of the normal postoperative appearance on MRI images after a meniscus repair is required to adequately assess potential complications [81 82]. Increased signal intensity passing the repair site on T2-weighted images, abnormal signal intensity adjacent to the repair site or dislocated fragments have been reported to be findings of a potential retear of the meniscus [81 83-85]. There are however also indications that MRI images might not be suitable for assessing healing after meniscus repair [86].

Figure 10. MRI T2-weighted sagittal image of the knee joint. The lateral meniscus has a bucket-handle tear with the posterior horn displaced anteriorly (arrow)

3.3 FUNCTIONAL TESTS

The clinical examination of the knee joint is important. Apart from the assessment of effusion, tenderness and range of motion, there are also specific additional tests to evaluate meniscus and ligament pathology.

McMurray's Test

With the patient in a supine position the examiner bends the knee and hip. With one hand on the knee, with index finger and thumb along the joint line, internal and external rotation of the lower leg is applied by the other hand. Pain or clicking sound may be noticed in a positive test. Sensitivity is reported to be about 55-70 % and specificity about 70-83 % [87 88].

Thesselay's Test

With the patient standing on the floor with weight on the affected leg and the knee in 20° of flexion, internal and external rotation in the knee is applied by twisting the upper body. Pain or sensation of locking or catching is a sign of positive test. Sensitivity is reportedly about 59 % and specificity about 67 % [89].

Apley's Test

The patient is positioned prone on the bed with the knee in 90° of flexion. A compressive force is applied on the patient's foot and the lower leg is externally and internally rotated by the examiner. This produces a compression on the menisci. Pain indicates a positive test. Studies report a sensitivity of about 60 % and specificity of about 70 % .

The Lachman Test

The patient is positioned supine on the bed with the knee in 30° of flexion. Assessment is performed in relation to the contralateral knee. The examiner isolates the thigh of the patient and the tibia is pulled forward. The amount of anterior translation and end stop is estimated. With an intact ACL anterior translation is prevented. A side-to-side difference of more than 2 mm is an indication of an ACL-injury [90 91]. Reported sensitivity ranges from 63 – 93 % and specificity from 55 – 99 % [92]. Quantification of anteroposterior laxity can be made by using the KT-1000 [4].

The Anterior Drawer Test

Placing the patient in a prone position with 45° of flexion in the hip and 90° of flexion in the knee with the foot flat on the bed. The examiner applies an anterior force on the tibia. A side-to-side difference is assessed, and an increased translation of the tibia relative to the femur indicates a positive test. The test is primarily used for assessment of ACL-injuries. Reported sensitivity ranges from 18 – 92 % and specificity 78 – 98 % [92]. The test is reported to be reliable for chronic conditions but not in acute situations [90].

The Pivot Shift test

The patient is positioned supine on the bed. The examiner applies a valgus stress and internal rotation of the tibia under axial load with the knee in full extension. The knee is then flexed. In a positive test the tibia is subluxated anteriorly relative to the femur in extension and reduced at approximately 30° of flexion [93]. The test is predominantly used for assessment of ACL-injuries. Grading of the subluxation is subjective why comparative studies are difficult [94 95]. Sensitivity is reported to range from 18 – 48 % and specificity 97 – 98 % [92].

4 OUTCOME

4.1 FAILURE

The reported failure rates for meniscus repair ranges from 0 – 40 % [18 96-99]. There are variations depending on method of fixation and perioperative characteristics. Successful rates around 80-90% are reported for both the previously used bio-absorbable arrows [50 100 101] and the all-inside sutures [52 99 102]. In a meta-analysis by Nepple et al. [103] from 14 cohorts with a minimum of 5-years follow-up the total failure rate was 23.1 %. Similar rates were noted for open, outside-in, inside-out and all-inside techniques, though the all-inside devices used were meniscal arrows only. There was a trend toward less failures for lateral repairs which has been reported in other studies [57 104 105]. In studies based on second-look arthroscopy, findings of partially healed meniscus repairs are reported. Ahn et al. [106] found 96.4 % of the patients to be asymptomatic but at second-look only 84.3 % were completely healed. Pujol et al. [107] found no difference in OA or clinical outcome for completely or partially healed meniscus repair and conclude that even a partially healed meniscus might retain its function.

4.1.1 TIMING OF SURGERY

There are few studies that have looked prospectively at time between injury and surgery. A recent study showed that early meniscal repairs had less failures than late repairs [108]. On the contrary, Yeo et al. [109] recently published a systematic review where they did not find any correlation between failure and time from injury to repair. They did however find better PROMs for patients undergoing surgery within three months from injury. This is in line with a study by Hupperich et al. [110] indicating superior outcome in terms of KOOS and Lysholm for short time between injury and surgery.

4.1.2 AGE AND GENDER

Based on the knowledge that most tissue degenerate over time, old age has been considered detrimental for the outcome after meniscus repair. Recent publications however indicate a lack of association between age and increased risk for reoperation [111 112]. Moreover, Hupperich et al. [110] found a strong correlation for higher age and superior outcome.

Regarding the gender perspective there are studies indicating higher failure rate for both men and women and no difference between the two [98 113 114]. Everhart et al. recently published a report indicating similar outcome in terms of PROMs for men and women [115].

4.2 OSTEOARTHRITIS AND MENISCUS PATHOLOGY

Osteoarthritis is a degenerative process where the articular cartilage is deteriorating leading to an increased inflammatory response with swelling and pain. The meniscus increases the weight bearing area and studies have shown that removal of meniscal tissue or its function might lead to an increase in peak contact pressure on the underlaying cartilage [116] and thus the development

of osteoarthritis [104 117-125]. In patients with an injury to the ACL, a simultaneous meniscus injury is associated with a higher risk for OA [118 126-128] and studies indicate that meniscus repair might have a preventive effect [125 129]. With this knowledge, an increasing focus on meniscal preservation has evolved [130 131].

4.3 KINEMATIC MEASUREMENT

There are several instruments for measuring muscle strength, and even though there are questions regarding the dynamometer's clinical relevance in sports and recreations it is regarded "gold standard". A validated dynamometer is the Biodex (Biodex Medical Systems Shirley, NY, USA) [132]. With the ability to measure isokinetic torque at different angular velocities and isometric torque at a number of fixed angles it has been widely used for patients with knee injuries. The patient is placed in the upright chair with the leg secured to a pendulum, and fully bends and straightens the knee for multiple repetitions. Both the strength of the hamstring and the quadriceps are measured. The injured or surgical side is objectively compared to the healthy side. As the patient is in a sitting position, the range of motion is limited to 0-100 degrees why evaluation of deep flexion strength is impossible.

4.4 INSTRUMENTED LAXITY – KT-1000

The KT-1000 arthrometer (MEDmetric, Corp., San Diego, CA, USA) is an instrument made for quantitative measurement of anterior knee joint laxity [4] and was used in *Study I*. The knee is placed in 30° of flexion and in neutral position with the foot on a footrest and a strap around the thigh. An anterior force of 20 pounds (89N), 30 pounds (134N) and manual max is used and the displacement of the tibia relative to the femur between the uninjured knee and the ACL-reconstructed knee is measured in millimeters. In *Study I* the 134N force was used. In a study on ACL reconstructed knees by Malcom et al the test-retest difference by the same examiner was within 2 mm, and the difference by two examiners in side-to-side difference on the same patients was 1.2 mm at 89N [133]. Detection of acute ACL injuries using the KT-1000 is reported to be around 50 % [134-136]. Sernert et al. [136] reported low sensitivity and fair reproducibility between examiners and emphasize that the same examiner should perform all laxity tests in clinical studies as there is a risk for variation between different examiners. In *Study I* an experienced physiotherapist was conducting a minimum of three measures with the maximum value registered. Patients with isolated ACLR, i.e. no meniscus injury, were compared to patients with ACLR and meniscus repair or resection. For the purpose of the study a side-to-side difference of >5 mm was considered a surgical failure.

4.5 PATIENT REPORTED OUTCOME MEASURE

From a surgical perspective it is common to evaluate success through radiographic investigation or by objective measurement of ROM, laxity or muscle function. In order to assess the patient's subjective outcome after knee surgery it is common to use self-administered questionnaires. Several different questionnaires have been developed [137-142], and one advantage of patient self-administration, as opposed to data collected through interview, is the reduced risk for introducing bias by the observer [143 144].

KNEE INJURY AND OSTEOARTHRITIS OUTCOME SCORE (KOOS)

The KOOS is a widely used questionnaire that was developed in the 1990s to assess patients' opinion regarding knee and associated disorders. It was initially intended to be used when the injury can be developed to OA. The instrument is an extension of the Western Ontario McMaster Universities Osteoarthritis Index (WOMAC) [145], a previous valid instrument for older patients with OA. The KOOS contains 42 questions in five different scales: Pain, other Symptoms, Activities of Daily Living (ADL), function in Sports and Recreation (Sport/Rec), and knee-related Quality of Life (QoL). A normalized score is calculated for each dimension, ranging from 0 to 100, where 100 represents the best result. The KOOS has been validated for patients undergoing meniscectomy and ACLR and can be used to measure changes over time [146-148]. The KOOS is an outcome measure in the SNKLR [149]. Worth noting is however that an acceptable score for the surgeon might not necessarily reflect the well-being of the patient. The KOOS was used in *Study II, IV, V*.

LYSHOLM SCORE

The Lysholm score focus primarily on complaints and symptoms but not functions in sport and recreations. It was originally developed in 1982 and revised in 1985 and comprises eight items with a total maximum score of 100. The eight items are: Limp (maximum 5 points), Support (5 points), Locking (15 points), Instability (25 points), Pain (25 points), Swelling (10 points), Stair climbing (10 points) and Squatting (5 points). Less than 65 points is regarded as poor, 65-83 fair, 84-94 good, and 95-100 excellent [137 150 151]. The Lysholm Score was used in *Study V*.

TEGNER ACTIVITY SCALE

The Tegner Activity Scale is an activity level scale that is being used to grade sport and work activities on a scale from 0 to 10 and is meant to be used in conjunction to the Lysholm score [137].

INTERNATIONAL KNEE DOCUMENTATION COMMITTEE (IKDC)

The IKDC developed this knee-specific instrument to evaluate the knee after an injury. It was one of the first developed and is considered one of the most reliable in its category. The original form comprises eight items: the patient's subjective assessment, symptoms, ROM, ligament

examination, compartment findings, donor site pathology, radiological findings and functional tests. The first four items are used for the overall final IKDC rating, and every point is rated A-D (normal to severely abnormal) [152].
A further development is the IKDC 2000 covering eleven items ranging from 0 to 100. It measures symptoms, function and sports activity and was used in the MOON-study on ACL reconstructions. It is a validated instrument but still has no normative data [152 153].

EQ-5D

The Euroqol 5-dimensions measures five dimensions of health including mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The instrument also contains a second part using a visual analogue scale for grading from 0 = worst imaginable health state, to 100 = best imaginable health state. The EQ-5D is available in more than 200 languages [154].

5 KNEE JOINT STABILITY

5.1 THE MENISCUS IMPORTANCE ON STABILITY

The meniscus does not only increase the load bearing surface and serve as a shock-absorber but also contribute as a stabilizer of the knee. Shoemaker et al. [30] performed a cadaveric study where they concluded that removal of a medial meniscus bucket-handle tear in an ACL-deficient knee caused the tibia to displace forward when a force was applied. Levy et al.[155], in similar settings, reported increased anterior tibial translation after a medial meniscus resection. Several biomechanical studies have confirmed these findings, and also give support to the fact that medial meniscus repair restore anterior tibial translation [156-160].

The lateral meniscus has been reported with less posterior wedge effect than the medial, and therefore potentially less importance for anterior tibial translation [28]. Musahl et al. [156] found that the lateral meniscus is important for stability during rotatory maneuvers in valgus load potentially implicating that a deficient lateral meniscus might results in a positive pivot shift. Following an ACLR a positive pivot shift is a risk factor for remaining instability and inferior PROMs [161 162].

5.2 ANTERIOR CRUCIATE LIGAMENT

The ACL is one of the ligaments of the knee and it is the main restraint to anteroposterior (AP) displacement of the tibia in respect to the femur. It is also of great importance for rotational stability [163]. The ACL is intraarticularly located, yet extrasynovially and is richly vascularized from the mid genicular artery [164 165]. It is mainly made up of parallel collagen type 1 fibers and glycoproteins, providing sufficient resistance against tension and load [166]. It runs from the medial wall of the lateral femoral condyle to the anterior intercondylar spine of the tibia [167] and is described to consist of two bundles, the anteromedial (AM) and the posterolateral (PL) [168 169]. The AM bundle is mainly tense from 30-90°, and the PL from 0-30° of knee flexion [167 170]. There are indications that the AM bundle provides better AP and rotational stability than the PL bundle [171 172].

The incidence for ACL injuries is approximately 68-80/100 000 persons/year in Sweden and globally [149 173-175]. Most injuries occur during non-contact situations such as cutting and landing in sports with soccer being the most common [176-179]. For patients sustaining an ACL injury the main goal is to reduce perceived instability [180]. Who will benefit from rehab alone or an ACL reconstruction is still debated [181-183] but high-activity athletes, especially individuals engaging in pivoting sports, are likely to profit from an ACLR. Recurrent giving way episodes might increase the risk for meniscus injuries why this could also be regarded an indication for ACLR [184 185]. Every month that passes after an ACL injury increases the risk for a meniscus injury [184]. Around 50% of all patients sustaining an ACL injury in Sweden undergo surgery [184] with patients aged 15-19 years being overrepresented [176]. The development of OA is still common regardless of treatment and many patients do not reach their pre-injury activity level [118 186-189].

5.2.1 ACL RECONSTRUCTION

To restore the ACL a graft is placed through drill holes in the tibia and the femur. The most commonly used tendons as autografts are the patellar tendon (BPTB), the hamstring tendon (HT) and the quadriceps tendon (QT). In Sweden the HT is the most frequently used graft [149]. Most studies provide comparable results for the different grafts in terms of stability [190-193]. HT grafts have been reported to result in less donor site morbidity compared to BPTB grafts [194-196]. Another option is to use allografts, which is rarely used in primary reconstructions in Scandinavia as studies indicate more re-ruptures, particularly for younger patients [197 198].

Previously the ACLR was performed using a transtibial (TT) technique, aiming for an isometric position. This led to a poor restoration of rotational stability [199-201]. Currently, the aim is an anatomical placement, commonly using the anteromedial (AM) portal technique [202-204] which has proven to provide superior rotational stability compared to the TT technique [205-207].

5.2.2 SWEDISH NATIONAL KNEE LIGAMENT REGISTER

There is a tradition of registers in Sweden since the mid 20th century. The Swedish National Knee Ligament Register (SNKLR) was established in 2005 by several ACL surgeons and covers more than 90 % of all ACL reconstructions performed every year. Demographic and pre- and perioperative data is collected, including information such as associated injuries, type of graft, graft dimension, antibiotics used, operation time etcetera. PROMs are collected preoperatively and at one, two, five and ten years postoperatively. The data is not collected in regard to any specific research question which potentially limits selection bias. A relatively common problem for any patient registry is loss-to follow-up. It is important to have good quality data to be able to draw any reliable conclusions. A threshold for validating the quality of a survey is a response rate of 60 % [208 209]. Furthermore, it is important to ascertain whether the respondents are truly representative for the specific group intended to be studied [210].

5.3 ACL AND MENISCUS REPAIR

In approximately 20 % of ACL reconstructions and revisions in Sweden a meniscal repair is being performed. The numbers have increased over the past decade [209]. Meniscal repair performed in conjunction to an ACL-reconstruction have been reported to be associated with less failure of the meniscal repair compared to isolated meniscal repairs [17 104-106 211 212]. One theory for the beneficial effect of ACL reconstruction on meniscal repair is the drilling of the femoral and tibial tunnel causing an abundance of growth factors in the joint postoperatively [212]. The initial moderate rehabilitation following ACLR might also contribute to a better healing environment for the meniscus. Moreover, meniscus tears in ACL-intact knees are possibly of a degenerative composition, whereas meniscus tears in conjunction to ACL injuries are more amendable to repair [103]. Nepple et al. [103] did however not find any difference in failure for meniscus repairs performed in ACL-deficient compared to ACL-intact knees.

6 MENISCUS TRANSPLANTATION

In situations where a meniscal tear is irreparable, for example some chronic bucket-handle tears, a total meniscectomy is still the only treatment available. Meniscectomy leads to an increased pressure on the underlaying cartilage (Figure 11).

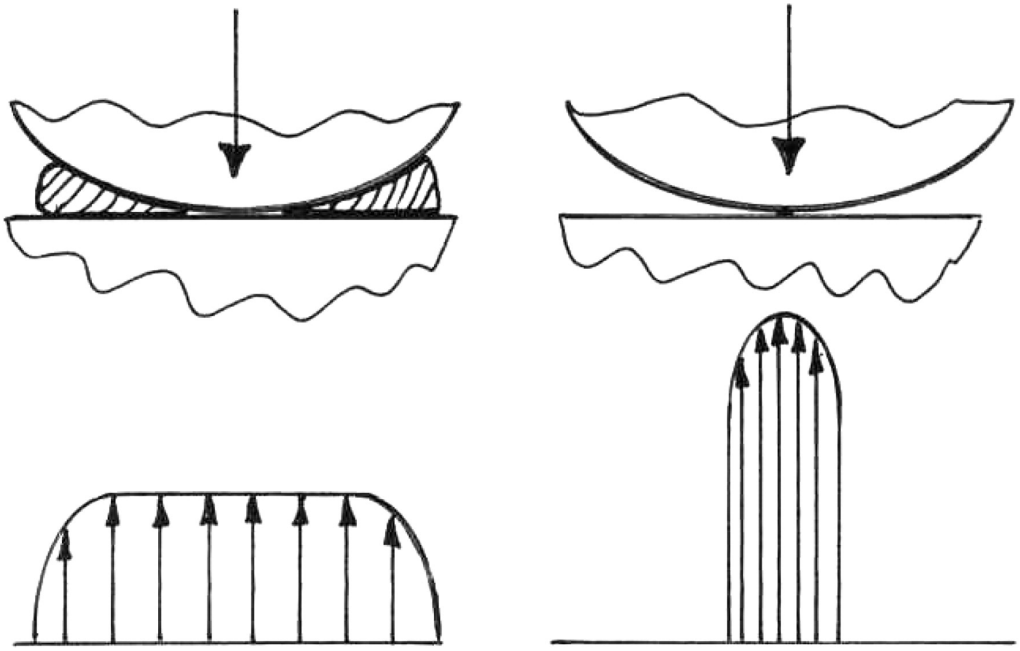

Figure 11. Schematic illustration of pressure distribution with intact meniscus (left), and with meniscus removed (right). (Reprinted with permission. McDermott et al. [213])

Medial meniscectomy can result in 50-70 % reduction in contact surface and 100 % increase in contact force on the underlaying cartilage. For a lateral meniscectomy the increased contact force can be as high as 200-300 % [1]. Because of this knowledge there has been a growing attention on potential substitutions for the removed meniscus.

6.1 SCAFFOLDS

In the nineties, scaffolds were introduced to support the regrowth of fibrocartilaginous meniscus tissue. There are currently two scaffolds available in the market. The Collagen Meniscal Implant (CMI®, Ivy Sports Medicine, Gräfelving, Germany) have been reported with 70 % successful outcome [214] and potential chondro-protective effects at 10-year follow-up [215]. Despite promising results, the CMI® is not widely used and not even available on the US market. The Actifit (Actifit®, Orteq Ltd, London, UK) degrades with time and has been studied in a multi-center study with 52 patients and two-year follow-up. Significantly improved knee function was noted, and MRI showed increased signal indicating tissue ingrowth in 82 % [216]. Both the CMI-Menaflex® and the Actifit® have been reported with similar outcome [217].

6.2 MENISCUS ALLOGRAFT TRANSPLANTATION

The first reported meniscal allograft transplantation (MAT) took place in Germany in 1985 [218]. The procedure has evolved over the last centuries, much through the work of pioneers in Europe, Asia and North America. Most meniscal allografts are today fresh-frozen, as recommended by the International Meniscus Reconstruction Experts Forum (IMREF) [219]. Even though this results in less viable cells, no adverse effects on clinical outcome or survival compared to fresh allografts has been shown [220]. One major advantage, compared to fresh allografts, is that fresh-frozen grafts can be stored for up to 5 years.

When MAT is used where required patient criteria are fulfilled, significant improvement in pain relief and function is reported [221-223] as well as approximately 80 % graft survival [224-226]. The typical failure involves a tear in the posterior horn of the graft [227]. Furthermore, the less OA present at the time of MAT the better the results [228]. Even with some promising results the chondroprotective effect of MAT remains unclear [222 229]. As a result, prophylactic MAT even in young patients with asymptomatic meniscectomized knees is presently not recommended [219].

The most suitable form of fixation of MAT has been debated. MAT with the bone fixation has been associated with improved load transmission and thus better healing [230-232]. When trans-tibial fixation is used however, Hunt et al. did not find any difference in pull-out strength for bone-plug or suture fixation alone [233]. This is in contrast to reports indicating less meniscal extrusion when bone-plug fixation is used [234-236].

In Sweden, meniscal transplant with allograft from tissue banks has not been a procedure performed at any greater scale and no center uses this method as a standard procedure. Moreover there are no tissue banks in Sweden for transplants meaning that all allografts need to be purchased from the US or Belgium at a substantial cost [237].

From an international perspective meniscal transplantation is a well-established treatment and no longer considered experimental. It is however still a rare procedure at about 1/1’000’000 population [219].

6.2.1 SEMITENDINOSUS TENDON

The semitendinosus tendon has been used as an autologous tendon transplant for reconstructive orthopedic procedures for the past 25 years. In Sweden it is being used as the graft of choice in 85 % of all primary anterior cruciate ligament reconstructions [209]. When a free tendon transplant with collagen tissue is needed in other reconstructive procedures such as augmentations of patellar tendon, quadriceps tendon, elongation of tendons the semitendinosus is a common graft [238-240]. The main reasons for its popularity are the relatively easy harvest, its low harvest morbidity and good tissue abilities [241 242]. There is usually a regeneration of the tendon after harvesting, though strength deficiency may remain for up to two years [241-247].

When using the semitendinosus as a graft for ACL reconstruction, the cells in the tendon gradually remodel into more ACL characteristics. The load and position of the transplant in its new milieu is thought to be the reason for the remodeling process [248].

Johnson and Feagin used tendon autografts as a meniscus substitute in a pilot study on a small number of patients in 2005 [249]. No preservation of the joint line or improvement in patient reported outcome was noted. However, the patients had severe OA and consequently a malalignment of the knee joint meaning they were waiting for a total knee replacement. The patients would never have been candidates for a conventional meniscus transplantation or substitution.

7 AIMS OF THE THESIS

STUDY I

The aim of study I was to evaluate ATT depending on type of treatment of meniscus injuries in conjunction to primary ACLR. The hypothesis was that the integrity of the meniscus is important for the function of the ACL graft and the persisting laxity following ACL reconstructions.

STUDY II

The aim of study II was to compare KOOS and EQ-5D at 2-year follow-up after isolated ACL reconstruction to ACL reconstructions with associated meniscus injury treated with either repair or resection in the Swedish National Knee Ligament Register. The hypothesis was that patients with a meniscus resection or repair would have worse outcomes in KOOS or EQ-5D subscales than those with an isolated ACL reconstruction.

STUDY III

The first aim of study III was to analyze the failure rate for meniscus repairs performed consecutively at two main clinics during a twelve-year period. The second aim was to study potentially predictive factors for failure. The first hypothesis was that meniscal sutures with anchors, lateral meniscal repairs and repairs performed concomitantly to an ACL reconstruction would have less failure than bioabsorbable meniscal arrows, medial meniscal repairs and isolated repairs. The second hypothesis was that younger patients and acute meniscus tears would have less failure.

STUDY IV

The aim of study IV was to determine the effect of meniscus repair on the development of OA and patient related outcome. The first hypothesis was that a successful meniscus repair would have lower risk for OA compared to a failed meniscus repair. The second hypothesis was that patients with successful meniscus repairs would have superior subjective knee function than patients with a failed meniscus repair.

STUDY V

The first aim of study V was to investigate if the semitendinosus tendon could function as a meniscus transplant following meniscectomy. The second aim was to study if patients receiving a meniscus transplant by semitendinosus tendon experience less post meniscectomy symptoms.

8 ETHICS

EXTERNAL RESEARCH ETHICS

Before the research project is initiated, an approval from an ethical committee is required.

The first two studies are based on data from the registries. Prior to participation the patients were given information and asked to give consent. The patient was also informed about the possibility to withdraw from the study and have all data removed from the list at any time. This is important in order to respect the principle of integrity and autonomy. To further protect the integrity of the individual, each participant receives a specific ID-number throughout the study. All individuals participating in a study must have a clear understanding of the purpose of the project and its aims.

The retrospective review of medical records is considered to pose a very limited risk for harming the patients. The participants in the study might feel intruded by the fact that we scrutinize a large amount of their charts in search for relevant data. Even though we strictly try to keep the search to only relevant parts of the medical record, there is a risk that the researcher encounters data not relevant for the study. The participants are however informed that they at any time can retrieve information on what data has been collected. The results are presented on group level why the risk for an individual to be recognized is nearly impossible.

For the patients participating in the follow-up part in *Study IV*, the questionnaires have previously been extensively used and are strongly validated, well-known instruments without any known side effects. Even so, it could be considered an intrusion in the patient's private life. Especially the questions regarding activity level and health related quality of life. The patients do also have the alternative to at any time opt out from the study.

For the patients also participating in the radiological part of the follow-up in *Study IV* the added radiation could theoretically impose an increased risk for radiation related disease. This dose is very low (0.01 mSv) and represent the average background radiation for a person in Sweden in a day. The risk is therefore very low why the principle of no-harm is considered fulfilled. Any patient who have developed osteoarthritis will be informed about this, which could cause an onset of anxiety for future symptoms. If the patient does not suffer from any symptoms related to osteoarthritis at the time, they can be presented to unnecessary suffering. The benefit of early diagnosis and therefore early treatment is however worth emphasizing.

For *Study V* there are some more risks to consider. As with many surgical procedures there are always a risk for infection or thrombosis. Prophylactic medication with antibiotics and antithrombotic will be administered.
The risk for the actual surgical procedure is that the meniscal transplant does not heal as planned and may thus require another surgical procedure. This does not differ from conventional meniscal transplant procedures. The semitendinosus tendon is a common

transplant in knee surgery. There is not considered to be any risk for tissue rejection as tendon transplants with collagen does not face the risk of antigenicity as mesenchymal tissue can do. No immunosuppressive treatment is therefore necessary.

INTERNAL RESEARCH ETHICS

Regarding internal research ethics there are several aspects to be considered. Some of the studies deals with the process of vast amount of data and require a high level of documentation which poses a risk for research misconduct. For one the main data could be purposely altered, and parts could be left out. During the statistical analysis the method could be adjusted to fit the hypothesis. To avoid this it is important to check with the original study plan.

The nature of register studies limits the risk for fabrication, as all data has already been collected. The data can also easily be collected once again. In the retrospective analysis there is always a risk that variables receive increased attention as the study proceeds, why it is important to have a clear research question and the outcome decided beforehand.

The SNKLR gets notified on and approves all studies making sure that two similar projects are not ongoing simultaneously. Most journals also use tools to assess whether any plagiarism could have occurred.

9 METHODS

9.1 STUDY POPULATIONS

STUDY I

Study I is a register study based on the local register at Capio Artro Clinic, Stockholm, Sweden. A total of 6529 patients who had underwent primary ACL reconstruction using hamstring tendon grafts during 2000 – 2015 were identified. Excluded were patients with a concomitant PCL injury, MCL injury requiring surgical treatment, LCL or PLC injury or meniscus injury not requiring treatment. Patients with a previous ipsi- or contralateral knee ligament reconstruction or lack of evaluable pre- and postoperative KT-1000 measuring were also excluded. From the population, a cohort of 4497 patients was eligible for analysis. The cohort was divided into groups depending on meniscus status, displayed in Figure 12. There were no patients with combination of resection and suture or both medial and lateral suture. Mean (SD) time from injury to surgical procedure was 14 (9.6) months. Mean age at surgery was 28 years (range 9-59). There were 2395 male and 2102 female patients. Baseline characteristics are presented in Table 2.

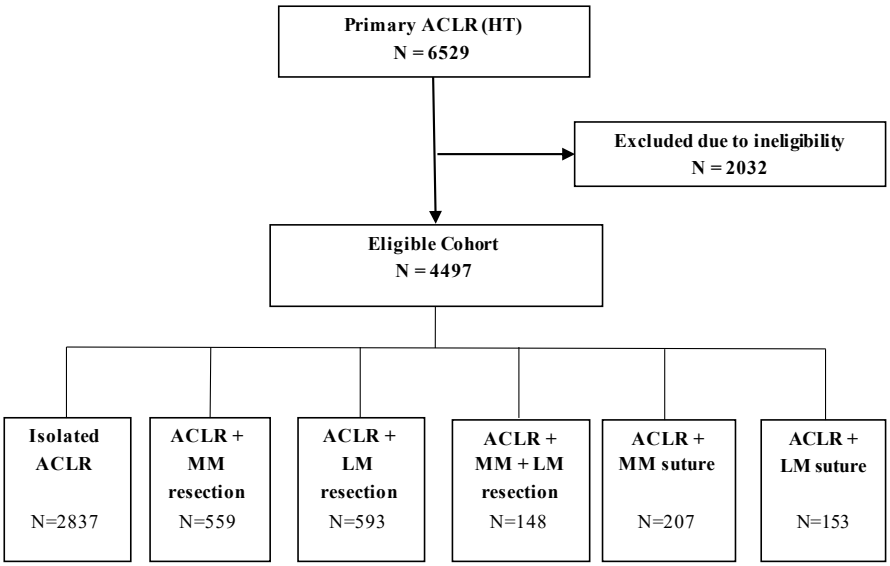

Figure 12. Patient flowchart for *Study I*.

TABLE 2
Demographic Characteristics for *Study I*

	Isolated ACLR	ACLR + MM Resection	ACLR + LM Resection	ACLR + MM + LM Resection	ACLR + MM Suture	ACLR + LM Suture
Number	2837	559	593	148	207	153
Age, y, mean ± SD	28 ± 10.5	32.8 ± 11	26.2 ± 9.6	32 ± 10.8	23.4 ± 9	20.7 ± 8.5
Male, N (%)	1439 (50.7)	342 (61.2)	360 (60.7)	93 (62.8)	87 (42)	74 (48.4)

Note: ACLR, anterior cruciate ligament reconstruction; LM, lateral meniscus; MM, medial meniscus; y, years

STUDY II

Study II is a register study from the SNKLR. In total 23062 patients were assessed using an *a priori* set of inclusion criteria: 1) ACLR from January 1st 2005 to December 31st 2014, 2) Age older than 12 years, 3) Primary isolated ACLR with autograft, 4) No revision ACLR or contralateral ACL injury, 5) No treated MCL or LCL injury, 6) No associated nerve- or vascular injury, fracture or tendon rupture. 7) Available KOOS and EQ-5D subscales at 2-year follow-up 8) No other meniscus surgery after ACLR. A total of 15392 patients were eligible for the analysis. The cohort was divided into groups depending on meniscus status, displayed in Figure 13. Baseline characteristics are presented in Table 3.

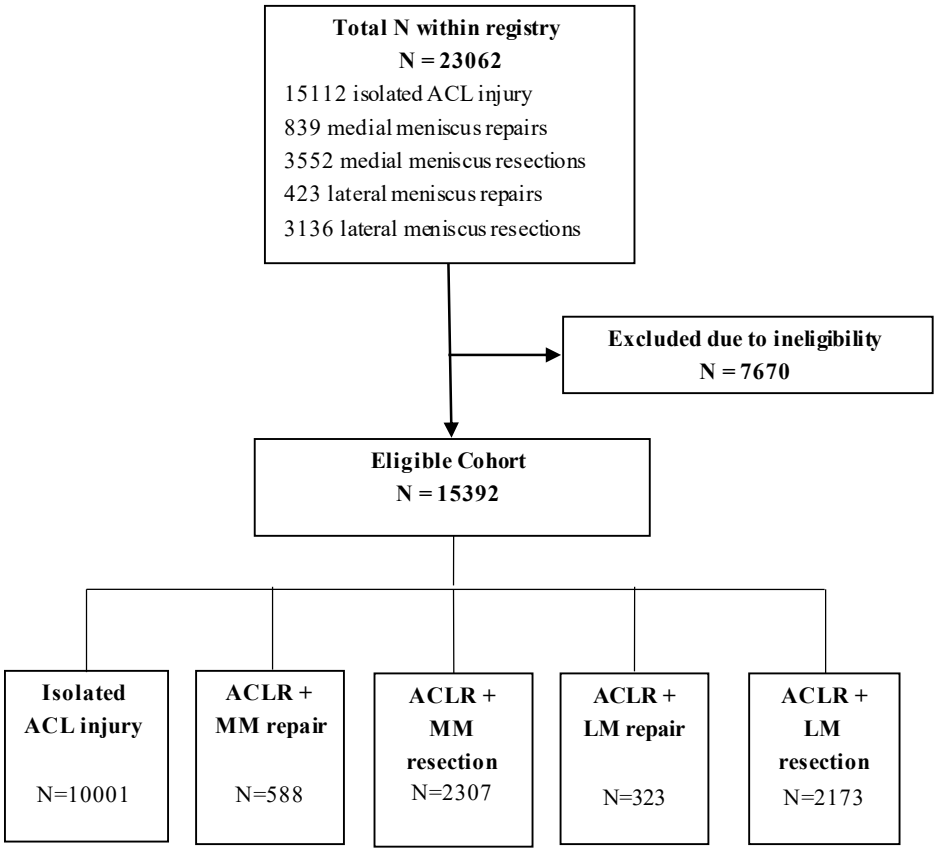

Figure 13. Patient Selection Flow Chart

TABLE 3
Demographic Characteristics for *Study II*

	Isolated ACL	ACLR + MM Repair	ACLR + MM Resection	ACLR + LM Repair	ACLR + LM Resection	Total N
Number	15112	839	3552	423	3136	23062
Male, N (%)	8227 (54.4)	411 (49)	2206 (62.1)	254 (60)	2124 (67.7)	13222 (57.3)
Age, y, mean ± SD	27 ± 9.8	24.7 ± 9.4	30.5 ± 10.9	22.3 ± 8.3	25.9 ± 9	27.2 ± 10
Days form injury to surgery, median (IQR)	239 (140, 452)	230 (127, 465)	390 (214, 892)	179 (99, 313)	225 (124, 443)	253 (143, 498)

Note: ACL, anterior cruciate ligament; IQR, inter quartile range; LM, lateral meniscus; MM, medial meniscus; y, years

STUDY III

In a retrospective medical chart analysis, patients who had an arthroscopic meniscus repair of a vertical, longitudinal tear performed at Capio Artro Clinic or Södersjukhuset, Stockholm, Sweden, between 1999-2010 and 1999-2011 respectively, were identified. Patient characteristics as well as intraoperative data was collected and is presented in Table 4. A total of 954 meniscus repairs were performed on 918 patients.

TABLE 4
Demographic and Intraoperative Characteristics for *Study III*

			Failed Fixation N		
		Total N (%)	No (%)	Yes (%)	*P* value
Number		918	711	207	
Age	Mean (Range)	26 (12-60)			n.s.
	<20	363 (39.5)	269 (74.1)	94 (25.1)	
	21-30	292 (31.8)	234 (80.1)	58 (19.9)	
	31-40	191 (20.8)	148 (77.5)	43 (22.5)	
	>40	72 (7.8)	60 (83.3)	12 (16.7)	
Gender	Female	382 (41.6)	298 (78)	84 (22)	n.s.
	Male	536 (58.4)	413 (77.1)	123 (22.9)	
Meniscus	Lateral	317 (34.5)	280 (88.3)	37 (11.7)	<0.001
	Medial	565 (61.5)	405 (77.1)	160 (28.3)	
	Both	36 (3.9)	26 (72.2)	10 (20)	
Repair method	Anchor	680 (74.1)	544 (80)	136 (65.7)	.004
	Arrow	226 (24.6)	157 (69.5)	69 (30.5)	
	Both	12 (1.3)	10 (83.3)	2 (16.7)	
ACL	No ACL injury	344 (37.5)	258 (75)	86 (25)	.015
	ACL injury, not simultaneously reconstructed	276 (30.1)	205 (74.3)	71 (35.7)	
	Simultaneous ACL reconstruction	298 (32.5)	248 (83.2)	50 (16.8)	
Days to surgery	Median (Range)	53 (0-3284)			n.s.
	0-30	377 (41.9)	291 (77.2)	86 (22.8)	
	31-90	159 (17.7)	115 (72.3)	44 (27.7)	
	90-365	261 (29.0)	199 (76.2)	62 (23.8)	
	>366	102 (11.3)	90 (88.2)	12 (11.8)	
Vascularization	Red-red zone		190 (74.8)	64 (25.2)	.044
Zone	Red-white zone		300 (80.2)	74 (19.8)	
	White-white zone		21 (63.6)	12 (36.4)	

Note: ACL, anterior cruciate ligament; n.s., non-significant

STUDY IV

Patients who had an arthroscopic meniscus repair of a longitudinal, vertical tear, performed at Södersjukhuset, Stockholm, Sweden during 1999-2011 were identified through retrospective medical chart analysis. In total, 318 patients were eligible for analysis. Two patients had bilateral meniscus repairs and only the first surgical procedure was included in the analysis. Flow diagram is presented in Figure 14. Baseline characteristics are presented in Table 5.

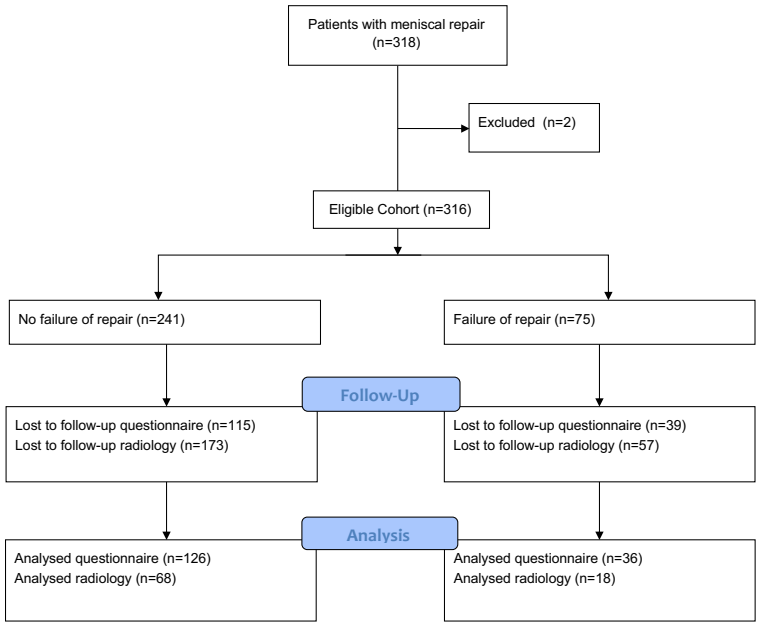

Figure 14. Patient flowchart for *Study IV*.

TABLE 5
Demographic and Intraoperative Characteristics for *Study IV*

			Failed Fixation		
		Total (n = 316)	No (n = 241)	Yes (n = 75)	*P* value
Age at surgery	Mean ± SD, yr	27 ± 9	27 ± 9	28 ± 9	n.s.
FU time	Mean ± SD, yr	9.3 ± 3.6	9 ± 3.7	10.4 ± 3.3	n.s.
Sex					n.s.
	Male	199 (63)	153 (76.9)	46 (23.1)	
	Female	117 (37)	88 (75.2)	29 (24.8)	
Meniscus					<0.001
	Lateral	106 (33.5)	96 (90.6)	10 (9.4)	
	Medial	197 (62.3)	136 (69)	61 (31)	
	Both	13 (4.1)	9 (69.2)	4 (30.8)	
Repair method					.011
	Anchor	147 (46.5)	123 (83.7)	24 (16.3)	
	Arrow	163 (51.6)	113 (69.3)	50 (30.7)	
	Both	6 (1.9)	5 (83.3)	1 (16.7)	
ACL					n.s.
	No ACL injury	131 (41.5)	96 (73.3)	35 (26.7)	
	ACL injury, Not simultaneously reconstructed	139 (44)	104 (74.8)	35 (25.2)	
	Simultaneous ACL reconstruction	46 (14.6)	41 (89.1)	5 (10.9)	

NOTE. Data are reported as number (percentage) unless otherwise indicated.
ACL, anterior cruciate ligament; n.s., non-significant; SD, standard deviation; yr, years.

STUDY V

Patients were assessed for eligibility according to an a priori set of inclusion criteria: Age 20-50 years old, previous history of total or subtotal medial or lateral meniscectomy, no significant OA changes on x-ray, +/- 3° varus/valgus alignment on HKA-projections, post meniscectomy symptoms (pain from affected joint line accentuated with weight bearing), no smoking, ligamentous stable knee (if ACL insufficiency ACL reconstruction was required). Between January 2018 and June 2020, seven patients were included.

9.2 SURGICAL PROCEDURE

Meniscus repair in *Study I-IV* was performed using arthroscopic technique in general anesthesia. Bioabsorbable meniscal arrows (Biofix, Bionx Implants) were the most common method of fixation up until 2004. From 2004 and forward the fixation technique was replaced by the second-generation devices with plastic anchors (FasT-Fix, Smith & Nephew; RapidLoc, DePuy Mitek, Sequent, Conmed; Viper, Arthrex). In most cases an all-inside device was used for ruptures in the posterior horn or mid-body of the meniscus, whereas repairs in the anterior horn of the meniscus was conducted using the outside-in technique. In *Study III-IV* there were no isolated inside-out or outside-in sutures in the analysis.

In *Study V* the semitendinosus was harvested through an incision over pes anserinus on the ipsi- or contralateral side . The flat end of the tendon was folded over the round part creating a double stranded loop and sutured with running 2.0 Fiberwire® embedding the round part with the knots in the free ends. A Chinese finger trap was created around the free strands of the graft. The graft length varied from 12 – 15 cm and 6 – 7 mm in diameter. The meniscus root guide was used to place the root tunnels as close to the anatomic position as possible. The graft was introduced through the accessory portal and the ends were pulled into the root tunnels using shuttling sutures. The new meniscus was fixed to the capsule using all-inside sutures for the posterior horn and inside-out and outside-in sutures for the mid-body and anterior horn respectively. Sutures were placed vertically.

Anterior cruciate ligament reconstruction was conducted arthroscopically in general anesthesia. In *Study I* all patients received a single-bundle autologous semitendinosus tendon graft. If the diameter of the graft was insufficient the gracilis tendon was added. Harvesting of the graft was performed in traditional fashion with incision over pes anserinus and the graft was quadrupled. In *Study II-V* the semitendinosus, bone-patellar-tendon-bone and quadriceps-tendon-bone grafts were used in some cases. Harvesting was made through traditional longitudinal incision. A transtibial or anteromedial portal technique was used for the drilling of the femoral tunnel, depending on the surgeon's choice. From 2005 the anteromedial portal was the predominant technique and comprises most of the cases. Fixation of the graft in *Study I* was performed on the femoral aspect using the EndoButton device (Smith & Nephew, Andover, Mass) and Ethibond n°5 sutures (Ethicon Inc, USA) tied over a post using a bicortical AO screw with a washer for fixation on the tibial side. Interference screws were used in a small number of cases. In *Study II-*

V tibial fixation varied. Cyclic loading of the graft was normally performed prior to tibial fixation. For cases of ACLR in Study V, the femoral part of the ACL graft was fixed before introduction of the meniscus graft.

9.3 REHABILITATION

Clinic specific rehabilitation protocols were used in the postoperative setting in *Study I, III, IV*. Following meniscus repair a hinged knee brace was used with ROM limited to 0-30° for two weeks, 0-60° for two weeks and 0-90° for two weeks. Full weight bearing was normally allowed. Avoidance of squatting was recommended for three months postoperatively. Following ACLR restriction to closed kinetic chain exercises was applied for the first three months. Return to sports was admitted depending on muscle strength and performance tests at the earliest 6 months following ACLR.

For *Study V* partial weight bearing was allowed for the first six weeks. A hinged knee brace was used, set at 0-30° for three weeks, 0-60° for three weeks, 0-90° for two weeks and unrestricted range of motion in the brace for another four weeks. Avoidance of squatting with weight bearing was recommended for the first four months.

10 STATISTICAL METHODS

All statistical analyses were conducted using IBM SPSS Statistics (SPSS Inc, Armonk, New York, USA). Statistical significance was considered at $p < 0.05$ and all tests were two-sided.

Chi-square test was used for categorical variables, and independent *t* test was used for continuous variables. For non-parametric or ordinal variables Mann-Whitney U test was used.

Linear Regression was used to compare KOOS and EQ-5D subscale scores between the meniscus groups and for comparison between associated procedure groups in *Study II*. The analysis was adjusted for patient age, gender and time from injury to surgery.

Logistic Regression was performed to estimate the risk for OA between meniscus groups in *Study IV*. One-way ANOVAs and post-hoc tests according to Tukey's HSD method was used to analyze the meniscus groups in *Study I*. ANOVA was also used to compare KOOS subscale scores between the meniscus groups in *Study IV*, and a factorial ANOVA was performed in *Study II* to compare KOOS and EQ-5D subscale scores depending on surgical technique.

Kaplan-Meier survival analysis was used to asses meniscus repair device survival and affecting factors were assessed using Cox Regression in *Study III*.

11 RESULTS

MENISCUS RESECTION INCREASES AND MENISCUS REPAIR RESTORES KNEE LAXITY (STUDY I)

The mean side-to-side difference in anterior laxity was reduced from 3.6 mm (SD 3.1) preoperatively to 1.9 mm (SD 2.2) for all patients (p=0.0001). There was a significantly greater laxity for the medial meniscus resection groups compared to isolated ACLR.

Stratification into three groups was made, based on KT-1000 in accordance with the IKDC knee examination form: ≤ 2, 3-5, and 5 mm. There were significantly more ACLR failures, defined as >5 mm, in the medial meniscus resection groups.

CLINICAL OUTCOME DEPENDING ON MENISCUS REPAIR (STUDY II & IV)

There was a significant difference in KOOS symptoms subscale between isolated ACLR and the meniscus resection groups ($\beta = -1.33$, p=0.022) in *Study II*. A significant difference in KOOS QoL subscale between isolated ACLR and the medial meniscus resection group ($\beta = -1.67$, p=0.031) was also noted. Furthermore, there was significant worse/inferior outcome in KOOS pain, ADL, sport/rec and QoL subscale scores for patients treated after 12 weeks of injury compared to patients treated within 12 weeks of injury.

In *Study IV*, KOOS symptoms (p=0.009), ADL (p=0.02) and sport/rec (p=0.041) were significantly better for successful meniscus repair. Significantly better Lysholm score was also noted for successful meniscus repair (p=0.036).

INCREASED FAILURE RATE FOR MEDIAL REPAIRS, REPAIRS WITH ARROWS AND ISOLATED REPAIRS (STUDY III).

The overall failure rate within three years in *Study III* was 22.5 %. There were significantly more failures within three years for medial meniscus repairs (p=0.001). Forty percent of medial meniscus repairs with arrows failed (p=0.009). Medial meniscus repair in conjunction to an ACLR resulted in significantly less failures (p=0.024). Survival functions are displayed in Figure 15-17.

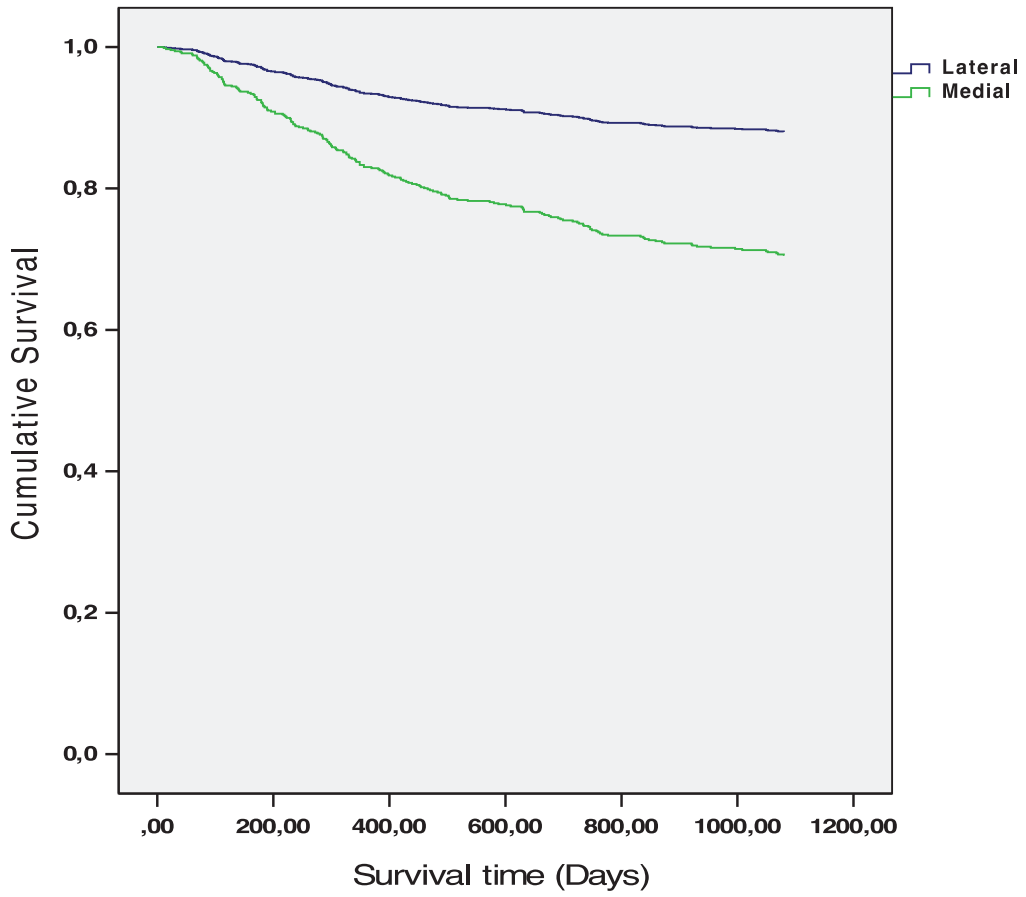

Figure 15. Survival function for medial versus lateral repairs.

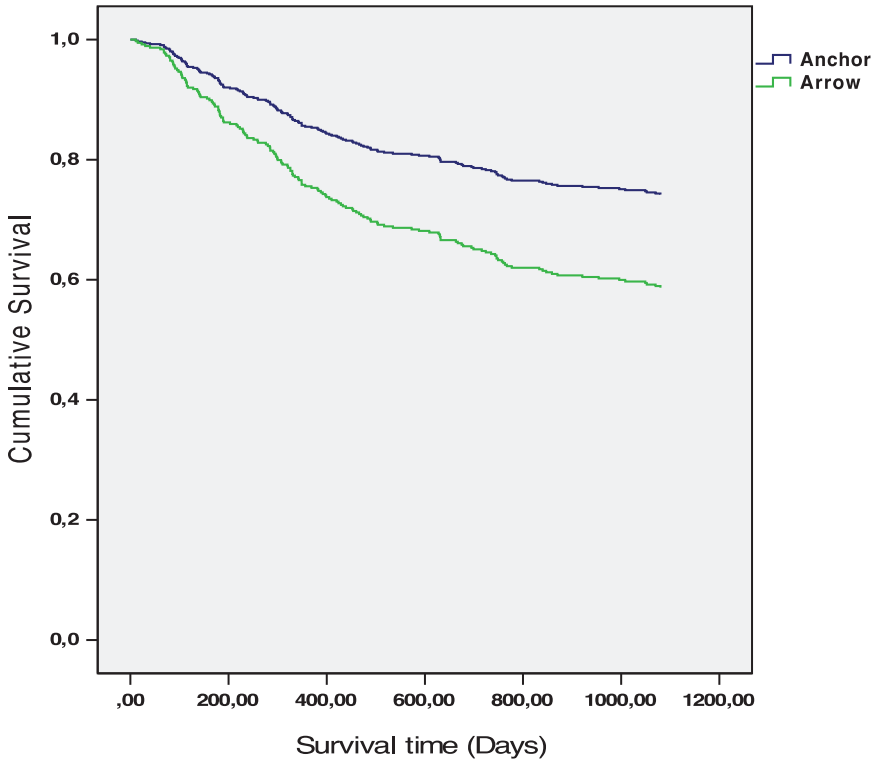

Figure 16. Survival function for medial anchors versus arrows.

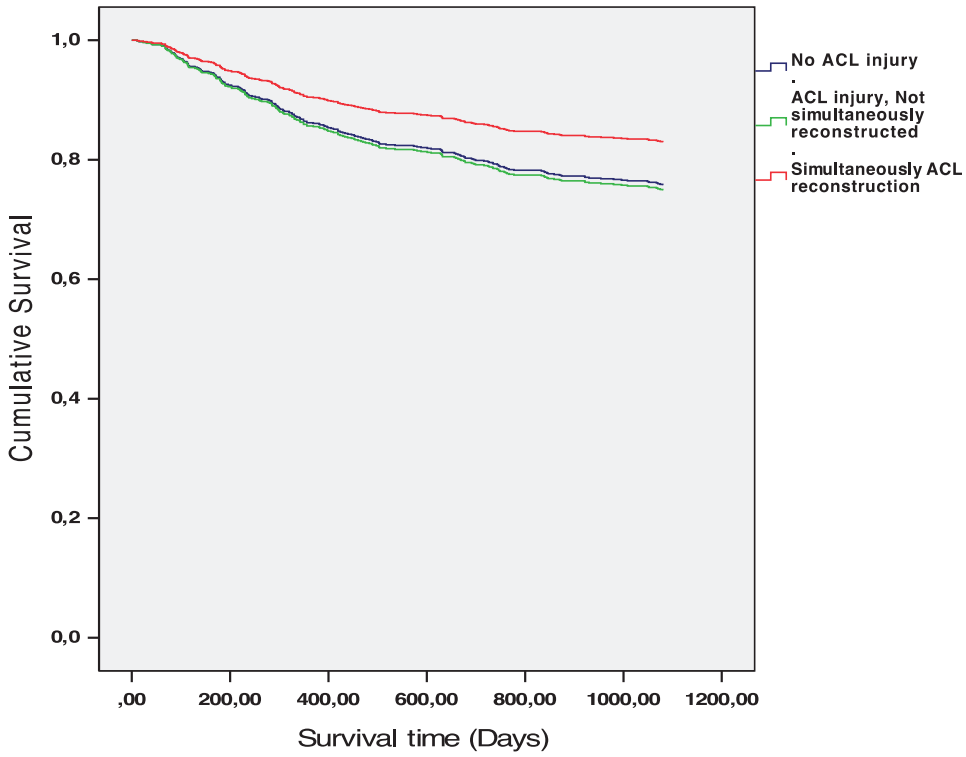

Figure 17. Survival function for medial meniscal repairs in association with ACL.

FAILED MENISCUS REPAIR INCREASE THE RISK FOR OSTEOARTHRITIS

In *Study IV*, 26.7 % of the patients had developed OA in the index compartment. Adjusting for gender and age at the time of follow-up, the risk for OA increased with an OR of 5.1 (p=0.007) for a failed meniscus repair.

IMPROVED PATIENT OUTCOME AFTER MENISCUS TRANSPLANTATION

In *Study V*, four patients had completed the follow-up at twelve-months. IKDC Global score had improved significantly (p=0.004). KOOS improved for all subscales, with pain significantly improving (P=0.038). A significant improvement in Lysholm was also noted (p=0.005). There were no major complications such as DVT or infection.

12 SUMMARY OF PAPERS

STUDY I

INTRODUCTION

The effect of meniscal repair on knee laxity in conjunction to ACLR is still debated. The purpose of this study was to investigate the effect of meniscus repair or resection in the setting of an ACLR. The hypothesis was that a medial meniscus resection would increase knee laxity compared to isolated ACLR, whereas a medial meniscus suture would contribute to laxity comparable to an isolated ACLR. It was further hypothesized that status of the lateral meniscus would not affect knee laxity.

MATERIAL AND METHODS

In total, 4497 patients with primary hamstring tendon ACLR were identified in the local database. Instrumented laxity was measured preoperatively and at 6-months follow-up using the KT-1000 arthrometer with 134-N load. Isolated ACLR was used as a control group to compare ACLR in combination with meniscus status.

RESULTS

A significant reduction from pre- to postoperative laxity was found for all patients ($p<0.0001$). Significantly increased laxity was found for the meniscus resection groups compared to isolated ACLR ($p<0.05$). Laxity comparable to isolated ACLR was found for the medial meniscus repair group. No significant difference in laxity was found depending on lateral meniscus status.

CONCLUSION

In conjunction to an ACLR, medial meniscus resection increased knee laxity whereas medial meniscus repair result in comparable laxity to isolated ACLR. Lateral meniscus resection or repair did not impact knee laxity.

STUDY II

INTRODUCTION

Outcome after meniscus repair or resection in conjunction to primary ACLR still lacks evidence. The purpose of this study was to compare KOOS and EQ-5D subscale scores at 2-year follow-up after primary isolated ACLR and ACLR with meniscus repair or resection in the SNKLR.

MATERIAL AND METHODS

From the SNKLR, all ACLR's with 2-year follow-up were reviewed including KOOS and EQ-5D subscales. Four groups were created: isolated ACLR, ACLR + medial meniscus resection, ACLR + lateral meniscus resection, ACLR + medial meniscus repair and ACLR + lateral meniscus repair and analyzed using linear regression. Subgroup analysis for time between injury and treatment and associated injuries was conducted.

RESULTS

Mean age was 27.2 years and 57.3 % were men. KOOS symptoms subscale scores were worse for medial and lateral meniscus resection. KOOS QoL subscale scores were worse for medial meniscus resection. There was no difference between isolated ACLR, and the meniscus repair groups.

CONCLUSION

Worse clinical outcome was found for meniscus resection in conjunction to ACLR compared to isolated ACLR, whereas meniscus repair presented similar results as isolated ACLR.

STUDY III

INTRODUCTION

The failure rate after meniscus repair ranges from 0-40 % with most reports based on small number of patients. The purpose of this study was to review all meniscus repairs during a 12-year period. The hypothesis was that repairs with anchors, lateral repairs and repairs performed during an ACLR would have less failures than repairs with arrows, medial repairs and isolated repairs. Younger patients and repair of acute tears was also hypothesized to have less failures.

MATERIAL AND METHODS

All consecutive meniscus repairs from two centers were analyzed retrospectively. Primary outcome was failure of repair within three years. Repair survival was assessed with Kaplan-Meier analysis and Cox regression.

RESULTS

A total of 918 patients had 954 meniscus repairs performed. Mean age was 26 years (range 12-60) and 58 % were men. The total failure rate in the cohort was 29 %. There were significantly more failures for repair with arrows than anchors (HR 1.8 [1.2-2.5]; p=0.009). Repairs on the medial meniscus had significantly more failures than repairs on the lateral meniscus (HR 3.7 [2.3-6]; p<0.001). ACLR in conjunction to a medial meniscus repair resulted in less failure than isolated meniscus repairs (HR 0.5 [0.3-0.9]; p = 0.009).

CONCLUSION

Repair on the medial meniscus results in significantly more failures than repairs on the lateral meniscus, especially when using arrows. Meniscus repairs in conjunction to ACLR had significantly less failures than isolated meniscus repairs.

STUDY IV

INTRODUCTION

Meniscus repair is reported to have better long-term outcomes compared to meniscus resection, possibly due to a higher risk for OA with meniscus resection. The purpose of this study was to study the effect of meniscus repair on OA and patient related outcome for meniscus repair.

MATERIAL AND METHODS

All patients who underwent meniscus repair during 1999-2011 at a clinic were identified from the local database and medical charts reviewed retrospectively. Questionnaires including KOOS, Lysholm and Tegner activity level were sent out. Patients were encouraged to undergo radiographic evaluation. Assessment according to Kellgren-Lawrence was conducted. Primary outcome was to determine the effect of meniscus repair on OA and secondly to study its effect on subjective knee function.

RESULTS

A total of 316 patients were included. Mean follow-up time was 9.3 years (SD 3.6). 51 % of the patients responded to the questionnaire, and 27 % completed the radiographic investigation. Women were overrepresented responders to the questionnaire ($p=0.010$) and the radiographs ($p=0.003$). Significantly worse KOOS symptoms ($p=0.009$), ADL ($p=0.02$) and sport/rec ($p=0.041$) was found for failed meniscus repair. Lysholm was significantly worse in the failed repair group ($p=0.036$). The risk for OA increased with an OR of 5.1 ([1.6-16.8]; $p=0.007$) for failure of meniscus repair.

CONCLUSION

Failed meniscus repair increased the risk for OA in the affected compartment and also the patients subjective knee function. This indicate that the meniscus is an important protector of the cartilage in the knee.

STUDY V

INTRODUCTION

Meniscus resection is reported to increase the risk for OA. In cases of meniscectomy, the alternatives for substitution are not widely available. The semitendinosus tendon has been used as a graft for ACLR for many years and is known to remodel and revascularize. The purpose of this study was to determine if the semitendinosus tendon can function as a meniscus transplant.

MATERIAL AND METHODS

An *a priori* set of patient inclusion criteria were used to assess patients for eligibility: Age 20-50 years old, previous history of subtotal or total meniscectomy medially or laterally, no significant osteoarthritic changes on x-ray (Ahlbäck 0-1), alignment on long alignment films producing hip-knee-angle (HKA) on x-ray maximum 3 degrees increased stress the affected compartment, post meniscectomy symptoms (i.e. medial or lateral pain accentuated with weight bearing), no smoking. In cases of ACL insufficiency a concomitant ACLR was performed. Surgical technique is thoroughly described in original paper.

RESULTS

Between January 2018 and June 2020 a total of seven patients have been included were six patients had a medial transplant and one had a lateral transplant. Mean age was 29 years. Four patients had completed the 12-month follow-up. Significant improvements were found for IKDC Global Score (p=0.004), KOOS pain subscale (p=0.038) and Lysholm (p=0.005). No surgical or postoperative complications were registered.

CONCLUSION

This is primarily a technical report, though the follow-up data give indications that the transplant survives, and most of the patients seem to improve in terms of pain and quality of life.

13 LIMITATIONS

There are several limitations present in the studies included in this thesis. First and foremost, four out of five studies (*I, II, III, IV*) are retrospectively conducted. The lack of randomization opens up for potential selection bias. The imbalance in the different groups has been assessed by conducting various analyses of baseline data. The large number of cases in the studies do however reduce the impact of potential biases. Furthermore, the retrospective design lacks the possibility of blinding. Patient reported outcome in a non-blinded setting has a potential to introduce reporting bias. There is also a risk that the patients included in the studies, have had a previous surgical procedure to the same, or the opposite knee without us knowing it.

Another limitation is that only medical charts from our local database was analyzed in *Study III – IV*. Knowing that patients are prone to contact the same clinic again, it is still possible that patients would seek consultation somewhere else over time. The failure rates reported could therefore be higher. Patients who answered the questionnaire have provided information on additional visits at other clinics, but for the non-responders it remains unclear. The large loss-to follow-up in *Study IV* is a major limitation on its own. Even though the non-response analysis indicates that the groups are similar and that the SNKLR also reports 50 % loss-to follow-up after more than one year it is problematic.

A limitation is the analysis of the surgical techniques used in the different studies. In *Study I – IV* it was not possible to perform an analysis of the different surgical techniques for drilling of the femoral tunnel or fixation of the graft during ACLR. This is due to lack of information as a consequence of the study designs. This could potentially affect the knee laxity in *study I*, the failure rates in *Study III* and the outcome reported in *Study II* and *IV* as well as the OA development in *Study IV*.

Furthermore the meniscal repairs included in the first four studies are poorly described. In *Study I – II* the report is gathered from the database and no information on location, length or vascular zone is included. In *Study III – IV* the medical charts have been reviewed but even so the description of such details is often scarce. No general classification of the meniscus tears has been used and neither any strict criteria as to what injuries or what patients should undergo a meniscal repair or not.

The heterogeneity of the studies with different surgical techniques, different devices and a large number of surgeons can be considered a limitation in its own, but it can also be argued that it therefore represents a clinical reality.

The location and the length of the meniscus tear was not known in *Study I.* It is therefore not possible to determine if a minimum amount of meniscus tissue needs to be resected to create an increased knee laxity. It is not possible to determine if a specific part of the meniscus has a greater importance on laxity of the knee. Furthermore, the purpose of study I was to analyze the anterior knee laxity. There are theories that the lateral meniscus is important for pivoting stability which could potentially be detected with the use of the pivot shift test. This data was however not available for analysis.

For *Study V* an obvious limitation is the short follow-up time and the limited number of cases, and thus the difficulty in drawing any major conclusion on graft integrity.

It is important to consider the clinical importance of the studies. In *Study II* the results are statistically significant, but the difference in actual numbers is very small why the relevance for the patient remains unclear. One possible explanation could be that the large sample size allows for statistical significance without a clinically meaningful difference. The clinical importance of the results in *Study V* can also be questioned. One-year follow-up is a short time for such an advanced surgical procedure and longer follow-up is needed.

Moreover the lack of information on smoking in *Study III – IV* is a limitation. Smoking is reported to increase the risk for early failure after meniscus repair [250].

We did not have any information regarding BMI in *Study III – IV* which is another limitation. Even though the samples in most studies consist of young individuals likely sustaining their injuries in sports activities, it is worth to consider that BMI could potentially influence the outcome. Sommerfeldt et al. did however not find any increased risk for meniscus repair failure for patients with a BMI >25 compared to BMI <25 [251]. The SNKLR includes data on BMI but the SNKLR was initiated in 2005 and *Study III – IV* goes back to 1999, and the studies also include isolated meniscus repairs as opposed to the SNKLR that only includes meniscus repairs performed in conjunction to ACLR. For *Study IV* the lack of BMI could potentially also affect the development of OA [252]. There is also a limitation that there was no restriction on BMI in study V. One patient in the *Study V* had BMI > 35 which can possibly affect the transplant integrity and development of OA.

There is a limitation in that data on rehabilitation was not available in *Study I – IV.* The patients followed more or less standardized rehabilitation protocols, but individual adjustments are made by the physiotherapists.

14 ADDITIONAL RESULTS

In *Study III* age was not significantly correlated to failure of meniscal repair. Kaplan-Meier function is presented in Figure 18.

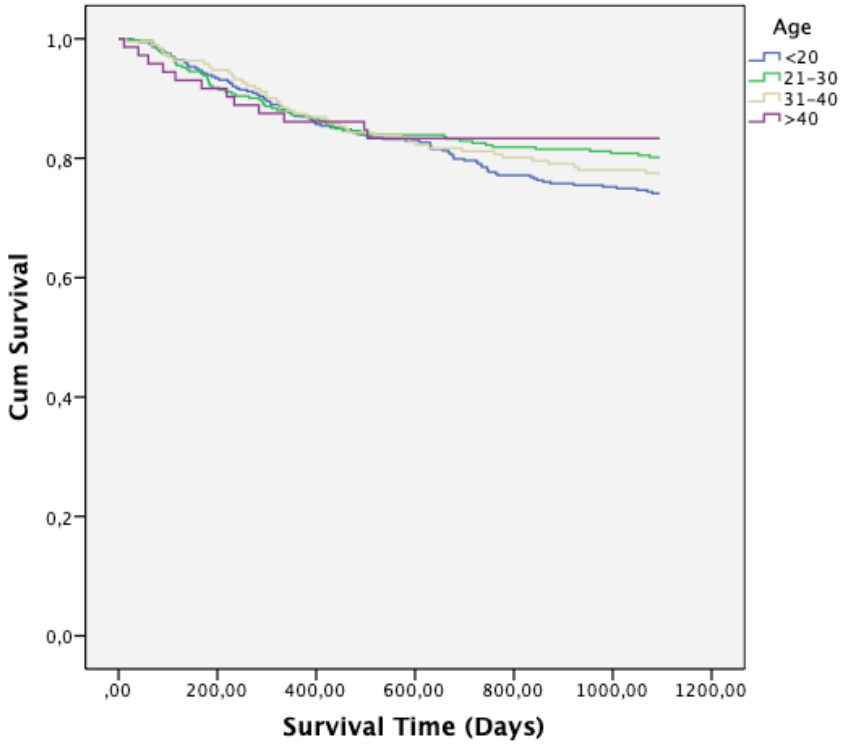

Figure 18. Survival function for meniscus repair in different age-groups.

The number of fixations for the meniscus repair was also considered in *Study III*. The univariate cox regression analysis is presented in Table 9. As the univariate analysis was not statistically significant the variable was not included in the multivariate analysis.

TABLE 9
Number of Meniscus Repair Fixations in *Study III*

		HR (95% CI)	*p*-value
	N (%)		0,416
1-2	600 (65)	1	
3-4	274 (30)	0,856-1,452	0,421
5-6	37 (4)	0,617-2,091	0,682
7-12	7 (0,7)	0,772-7,590	0,130

Note: CI, confidence interval

15 GENERAL DISCUSSION

15.1 FACTORS AFFECTING FAILURE AFTER MENISCUS REPAIR

The main goal of a meniscus repair is to maintain the protective effect of the knee joint. The healing of the repair is therefore important. For the clinician it is relevant to be able to present realistic expectations for the patient, and to be able to take relevant precautions to improve the healing potential.

Meniscus repair has been under constant development over the past decades. The possibility to perform meniscal repair arthroscopically reduced operation time and the morbidity in terms of smaller incisions and shorter recovery time [50]. The inside-out techniques used in the beginning required incision and retractors especially when repairs in the posterior part of the meniscus was conducted. There was still a risk for neurovascular damage why the all-inside techniques were developed. To begin with the all-inside devices comprised the bioabsorbable arrows [62]. Reports appeared of unsuccessful healing [63 64 68] and also potential cartilage damage [65 66] why the all-inside devices with mattress sutures over plastic anchors deployed behind the capsule were invented.

Before discussing the factors affecting failure following meniscus repair it is relevant to go through the various definitions of failure. In a recent publication by Yeo et al. [109] three different definitions for failure were described: 1) need for reoperation, 2) clinical failure according to Barrett's criteria [253] (joint line tenderness, joint effusion, locking or pain during meniscus tests), 3) failure determined by second-look arthroscopy according to Henning's criteria [254]. In studies where the symptoms alone are used as a definition for failure, higher number of failures might be found than when subsequent meniscectomy is required. Some studies use an MRI or second-look arthroscopy to detect potential failures [255]. In this case asymptomatic or partial failures might be detected. Pujol et al. [107] have concluded that even partially healed meniscus repairs might prevent future development of osteoarthritis and therefore be clinically relevant. In *Study III* a need for reoperation with subsequent partial or total meniscectomy was used as definition for failure. This could potentially result in an underestimation of failures. Even though our results cannot make any conclusions regarding partially healed menisci, in the light of the study by Pujol et al it seems relevant to rather leave an asymptomatic, potentially partially healed meniscus than to remove it.

The reported failure rate in the literature, ranging from 0-40 %, possibly reflect the different definitions of failure, in addition to the various associated factors. The overall failure rate in *Study III* was 22.5 % which is in line with previous publications [50 52 98 100-103]. The time frame of failing meniscal repair is also relevant to discuss. Analysis of long-time failure rates is demanding as it increases the risk of introduction of other factors than the actual healing itself. The difficulty to distinguish a failed healing from a new trauma gets additionally challenging over time. Studying the survival function of the total number of failures in *Study III*, the

impression is that most failures occur during the first three years. Based on this we believe that the assessment of failures is clinically most relevant within three years. Failures after this time frame could possibly be dependent on other factors such as biological deficiencies or simply a new trauma.

Another aspect when discussing failure is to what extent the failure comprises the original repair. It is not rare that when encountering a failed meniscus repair, only a part of the repair has failed leaving the remaining part intact. Pujol et al. [120] showed that meniscectomy after meniscus repair only extended the original tear in 13.5 % on the medial side and never on the lateral side. Having to resect a small flap tear in the posterior horn after suturing a complete bucket-handle tear is not necessarily a failure in terms of meniscus function preservation. Using strict definitions, such as in many registries where it is only possible to choose resection or repair, it would still be regarded a failure when in fact partial failure, or partial healing, would be a more accurate classification.

The increased failure rate for the first-generation repair devices with Biofix arrows has been reported to be 3.6 times higher than for FasT-Fix sutures [71]. The data in *Study III* is simply a confirmation based on a large number of cases.

The medial and the lateral meniscus are anatomically different as described in the introduction. In *Study III* nearly four times higher risk for failure on the medial meniscus was found. Favorable results for lateral meniscus repairs have previously been described [104]. The greater mobility of the lateral meniscus potentially makes it more forgiving for stress. Smigielsky et al.[10] has made some very detailed cadaveric dissections, and also present interesting theories on why repair of the posteromedial corner of the medial meniscus might fail. According to their study the posteromedial aspect of the medial meniscus only attaches inferiorly to the tibia. As the surgeon sutures the meniscus to the posterior capsule a reduction in mobility of the posteromedial corner might result in an increased tensioning of the structures during flexion and extension. We have in our research group made observations in the posteromedial compartment after all-inside repair and can from this combined extensive clinical experience, on an anecdotal level provide support to this theory. The insertion of the semimembranosus tendon at the posteromedial capsule could further distract the meniscus at the meniscocapsular junction contributing to a failure in cases of excessive tightening of the tissue [158].

Performing a meniscus repair in conjunction to an ACLR has superior results compared to isolated repairs [17 51 104 106 211]. One possible explanation is the richness in blood and thus an abundance of healing factors in the postoperative setting. The ACL reconstructed patient is also unavoidably more restrictive during the initial rehabilitation. Thirdly there is also a possibility that the isolated meniscus tear in a stable knee indicates biological deficits in the meniscus tissue, thus more susceptible to failure. A normal meniscus tissue would be able to restrain the force inflicted. There was no information in Study III regarding surgical technique. It is

plausible that a transtibial drilling would results in a greater rotational laxity and thus an increased stress on the lateral meniscus resulting in a higher failure rate.

The location of the tear has been reported to be of importance for the healing with peripheral tears in the red-red-zone having a richer blood supply with better healing potential [17 18]. Successful repairs of meniscus tears in the white-white zone are reported to be low [256]. In *Study III* no effect depending on vascularization zone was found. A third of the cases in the study did however lack information regarding vascularization zone. The reported vascularization zone might however be difficult to assess in most studies as the healing potential and thus the redness of the tear potentially could be overestimated by the surgeon once the decision of repair has been made.

There is a general belief that younger patients are more prone to successful meniscus repair. Based on theories that tissue degenerate with age it seems like a rational conclusion that younger age would be beneficial for meniscal repair, which has also been supported in the literature [257]. There are however several recent publications indicating a lack of correlation between age and failure of meniscal repair [17 71 111 253 258], and there are even studies indicating a higher risk for failure in younger patients [259 260]. In *Study III*, patients above 40 actually had less failures than the younger patients, though not statistically significant. A possible explanation for better results for older patients could be a more conservative case-selection by the surgeon and also that older patients have a lower physical activity level.

The chronicity of the tear and the effect on failure after meniscus repair has been debated. There are results indicating that repairs of chronic tears have similar failure rates as acute tears [261 262]. In *Study III* no correlation was found for failure and time between injury and surgery. Notably the data was highly right skewed with median 53 days and mode 5 days indicating that most patients were treated shortly after the injury whereas a few waited a long time. There are some aspects worth considering regarding chronic tears. A chronic tear might present with less symptoms, which is why surgery is not prioritized. The milder symptoms could be related to the chronic tear not being as unstable and thus have a better healing potential compared to the tear requiring prompt attention.

The orientation of the meniscus suture could also affect the outcome. Vertical sutures are reported to provide better stability and less failure than horizontal sutures [54-56 263-268]. As the majority of the collagen fibers of the meniscus are oriented circumferentially, a vertical suture will grasp a greater amount of the fibers and is with its perpendicular orientation less likely to cut through the tissue [269]. Not only the configuration of the suture is of importance, but also the direction of the two strands of the mattress, where a diverging direction might yield a better compression of the tear and therefore a better result [270 271].

The most common procedure when a meniscus repair fails is resection. In many cases the dislocated part of the meniscus is degenerated and not rarely of complex nature why revision

repair is not possible. In *Study III* only 1.5 % of the failed meniscus repairs were re-sutured. Fuchs et al reported acceptable results after revision repair [272] why this could possibly be considered in more cases.

The surgeon's experience, knowledge and training are factors that are difficult to quantify, yet not unlikely contribute to the outcome. In *Study III* there was no correlation between the number of surgical procedures performed or the failure rate. Though performing many surgical procedures does not necessarily indicate surgical skill, it seems reasonable to believe that performing many meniscal repairs would indicate arthroscopic experience.

15.2 MENISCUS REPAIR AND KNEE STABILITY

The importance of the medial meniscus for anterior knee laxity in the ACL-reconstructed knee has been studied in cadaveric models. Lorbach et al. [157] performed assessment of knee laxity by applying an anterior load of 134-N following ACL resection, medial meniscus tear, medial meniscus repair and ACLR. The ACL deficient knee with additional medial meniscus tear significantly increased anterior knee laxity. Repair of the meniscus injury and reconstruction of the ACL was able to restore comparable laxity to the intact knee. In contrast Papageorgiou et al. [160] found a medial meniscectomy to have no effect on anterior knee laxity. Results after cadaveric models must however be interpreted with care. The biological properties of the tissue in a cadaver are not necessarily completely comparable to living tissue and the absence of muscle contraction possibly affect the laxity of a joint [28 159 273-275].

In the ACL reconstructed knee, Kartus et al. [276] reported an increased laxity when using the Lachman test for patients with a deficient meniscus. On the contrary, Wu et al. [277] did not find any difference in laxity measured with the KT-2000 for intact or deficient menisci but did place stable non-repaired meniscus tears and repaired tears in the same group. In a long-term follow-up of 482 ACL reconstructions, Shelbourne and Gray [278] found an increased anterior knee laxity using the KT-1000 manual maximum for patients with a deficient meniscus.

The type and location of the meniscus tear might be of importance for anterior knee laxity. The posterior horn has been reported to be of greatest importance for stabilization and more than 75 % of patients with a meniscus injury in conjunction to an ACLR are located in the posterior horn [35]. In a cadaveric study by McCulloch et al. [273] a complete tear of the posterior root of the medial meniscus was needed to increase anterior knee laxity, whereas partial or subtotal meniscectomy did not make any significant changes.

With the medial meniscus being important for anterior knee laxity, the lateral meniscus has no "wedge effect" [28] and is also more loosely attached [2] and thus more mobile making it less prone to prevent anterior tibial translation. The lateral meniscus is however reported to be important for pivoting laxity [8].

The increased anterior laxity in meniscus deficient knees has also been reported to affect the graft after ACLR with increased forces in the graft of more than 50 % [160]. In biomechanical studies more graft failures have been seen in the meniscus deficient knee [159 160 274 275] as the altered kinematics increase the stress on the graft. In a clinical setting, Robb et al. [274] reported a 4.9 times higher risk for ACL graft failure with meniscus deficiency at 2-year follow-up. Failure was defined as a positive pivot shift, subjective rotational instability or MRI/arthroscopically verified rupture of the graft. This is confirmed in *study I* with significantly more surgical failures with medial meniscus resection in association to ACLR. Robb et al. further concluded that meniscus repair demonstrated similar graft failure rates, which is also confirmed in *Study I*.

The ACL and the medial meniscus work together in the stabilization of the knee with an ACL insufficiency causing an increased stress on the medial meniscus, possibly explaining the high prevalence of medial meniscus injuries in the ACL-deficient knees [156].

Worth mentioning is that measuring laxity after ACLR and meniscus surgery does not necessarily say anything about the patient's subjective outcome. Sernert et al. [279] have concluded that the KT-1000 does not correlate to Tegner Activity Scale and can therefore not be used as a predictor for return to sports after ACL surgery.

In *Study I* no adjustment was performed according to age. The patients in the repair groups were younger, and as there are studies indicating that young age is a risk factor for increased laxity after ACLR an additional analysis would rather have strengthened the findings [280 281].

15.3 PATIENT REPORTED OUTCOME AFTER MENISCUS REPAIR

A meniscus tear is a major injury to the patient and the recovery from meniscus repair is relatively long. The status of the meniscus influences the patient reported knee function. Lutz et al. reported better outcome in all KOOS subscales apart from QoL in favor of meniscus repair compared to meniscectomy [119].

In the setting of an ACLR an associated meniscus repair has been reported with both positive and negative short-term effects on patient reported outcome. Svantesson et al. [282] reported worse KOOS values at 1-year follow-up and Lysholm at 6 months follow-up for ACLR with concomitant meniscus repair. LaPrade et al. [283] similarly found worse KOOS symptoms and QoL subscales values at 2-year follow-up for meniscus repair in conjunction to an ACLR from the Norwegian ligament registry. Melton et al. [284] however reported poorer IKDC results for ACLR in combination with meniscectomy. Cristiani et al. [285] found no difference in any of the KOOS subscales at 1- and 2-year follow-up for ACLR and successful concomitant meniscus repair, but reported worse results for failure of the meniscus repair. Kimura et al. [286] reported excellent Lysholm score following meniscus repair. Both *Study II* and *Study IV* report better results for successful meniscus repair.

Regarding KOOS the sport/recreation and quality of life subscales are reported to be the most important for patients with a meniscus pathology [287]. Statistically significant values in KOOS does not necessarily mean that there is a meaningful difference for the patient. This has led to the discussion regarding the minimal clinically important difference (MCID) or minimal important change (MIC) which is the smallest change that is clinically important or noticeable by the patient. Roos and Lohmander [148] reported eight to ten points to be of clinical importance which was also found by Barenius et al. [118]. Ingelsrud et al. [288] did however find MIC values of 12 for Sport/Rec and 18 for QoL up to two years after ACLR, and noted that for the Pain, Symptoms and ADL subscales small changes were made between preoperative and follow-up measuring. In *Study IV* there was a difference of eleven points in the sports/rec subscale, indicating a clinical relevance. Worth mentioning is that there are currently no publications on MCID for meniscus repair.

Following ACLR there are suggestions for further defining successful outcome. Barenius et al. [289] have defined a functional recovery (FR) based on the lower 95 % confidence interval of KOOS from a Swedish reference population of 18-34-year old males. Reportedly only one fifth of patients reach functional recovery two years after ACLR. Another criterion presented by Muller et al. [290] is the so-called patient-acceptable symptoms state (PASS) where the patients answer a question regarding the state of their knee. In line with the MCID there are to date no further development of such criteria for successful outcome following meniscus repair.

In *Study II* meniscus repair provided similar outcomes as patients with an isolated ACL reconstruction whereas the KOOS symptoms and QoL subscales were significantly worse for meniscus resection at 2-year follow-up. This is conflicting with data presented by LaPrade et al. [283] on the Norwegian Knee Ligament Registry where no difference was found for 2-year follow-up scores regardless of meniscus status. The clinical relevance of the findings in *Study II* can however be questioned as the MCID were not fulfilled for any of the subscales. When conducting analyses on large samples there is a risk that even small differences of no clinical importance can be statistically significant.

Several previous publications have presented negative implications with meniscus resection [104 122 278 291]. The data from *Study IV* further support this in the long-term perspective, with significantly worse KOOS symptoms, ADL and sports/rec as well as Lysholm for patients undergoing meniscus resection. The data supports the importance of the meniscus for the knee joint and that a meniscus injury affects the patients' ability to participate in sports nine years after surgery. KOOS values for a reference population has been presented by Paradowski et al. [292]. When comparing the outcome of patients with a failed meniscus repair in *Study IV* it is obvious that the injury affects the patients knee function. It is however also obvious that the non-failed meniscus repair patients report worse outcome compared to the reference population.

The baseline data in *Study II* also presented worse preoperative scores for patients with a meniscus injury compared to patients with an isolated ACL injury which is in line with the finding by LaPrade et al [283].

The timing aspect of patient reported outcome was analyzed in *Study II*, where patients undergoing surgery later than 12 weeks from injury had worse results compared to surgery prior to 12 weeks from injury. In *Study II* all patients had a simultaneous ACLR. There are previous studies indicating a risk for arthrofibrosis when conducting ACLR in the early stage why delayed surgery has been advocated [293 294]. However in a recent publication by Eriksson et al. [295] no risk for arthrofibrosis with early ACLR was found.

15.4 THE EFFECT ON OSTEOARTHRITIS

The contribution of the meniscus in protecting the joint cartilage has been reported [122 276 278 296-299]. The risk for OA with meniscus resection was reported already in 1948 by Fairbank [75]. Meunier et al. [126] described the status of the meniscus as the most important factor for OA following an ACL injury. This was confirmed by Barenius et al. [118] who reported an increased risk for OA with an OR of 4.2 for medial meniscus resection and 5.1 for lateral meniscus resection. In *Study IV* a five-fold increased risk for OA was found for failed meniscus repair. Data indicate that the medial meniscus is of most importance though the number of cases in the sub-analysis of failed repair between medial and lateral meniscus are small. Previous studies have reported the lateral meniscus to be more important in preventing the development of OA [300-302]. This could possibly be explained by the fact that removal of the medial meniscus results in an increased contact stress by 100 %, whereas removal of the lateral meniscus results in an increased contact stress of 200 – 300 % [303]. Moreover there is an incongruence of the joint surfaces in the lateral compartment possibly also contributing to the development of OA in the absence of the lateral meniscus [23]. Findings supporting the importance of the medial meniscus for the development of OA was reported by Higuchi et al [304]. During running and standing a great amount of the weight force is planted through the medial compartment, depending on the individual mechanical alignment [305]. In *Study IV* no data on mechanical alignment was available. Thus, we do not know whether the mechanical axis was running through the affected compartment or not which could be a potential factor in both the development of OA and patient related knee function.

Though not as strongly correlated as failed meniscus repair, age was also associated to the development of OA in *Study IV*. This is not surprising as the relationship between aging and OA is well established [306].

As reported in *Study I* the medial meniscus is a secondary stabilizer in the knee joint, possibly also affecting the development of OA. From a theoretical perspective an increased laxity in the knee joint could cause an increased grinding of the joint surfaces. Inadequate restoration of knee

laxity has previously been described as a predictor for future OA, possibly due to a residual positive pivot shift [188].

Not specifically studied in this thesis is the effect of chondral injuries on the development of OA. It has however been reported that the meniscus is important in the setting of cartilage repair, indicating that some sort of concomitant meniscus transplantation could be appropriate in cases without a functioning meniscus [307].

15.5 SALVATION FOR LOST FUNCTION?

The challenge of appropriate treatment for young patients with post meniscectomy symptoms is apparent. Different meniscus substitutions have evolved over the past decades [308-310].

The biodegradable synthetic scaffolds have been extensively used [311]. Second-look arthroscopies indicate a meniscal tissue regrowth and patient related outcomes are superior to meniscus resection. The argument against the use of scaffolds is their lack of biological properties. Despite early promising results and possibly due to inferior long-term results [214 216], scaffolds are not widely used today.

There are studies reporting results of success after MAT [221 312-315]. The problem with sizing, availability and cost is a hindrance in the widespread use of meniscal allograft transplantation [237]. These are reasons why the use of MAT in our country is low, and thus the patients in *Study V* were not offered MAT as an alternative treatment. As mentioned, MAT is still a rare procedure with 1/1'000'000 population being performed [219].

The idea of using a tendon as meniscal transplant has been presented before. The peripheral part of the meniscus is described to be histologically tendon-like [316]. Mejias et al. [317] presented a case-report where they used a semitendinosus autograft as a medial meniscal rim replacement in a 32-year old, varus morphotype patient with post meniscectomy symptoms. Five months later a second arthroscopic surgery was performed where the transplant was synovialized and stable. A meniscal scaffold was subsequently attached to the new rim. At 2-year follow-up the patient was pain free and had a Lysholm score of 92. Kohn et al. [318] used the patellar tendon as a meniscus transplant in an animal Study and noted a remodeling of the tissue. They also performed a study using part of the quadriceps tendon as meniscal transplant in patients. Both healing and cartilage protection was successful and though twelve-month data looked promising no detailed data has been published [319]. Johnson and Feagin on the contrary did find non-favorable results after using semitendinosus and patellar tendon autografts as lateral meniscus transplants [249]. They reported no preservation of the joint space or clinical improvement. The five cases in the study did however have a severe loss of lateral joint space and profound genu valgus prior to the transplant procedure why they could rather be considered candidates for knee replacement. With a relatively advanced OA, a meniscus transplant is unlikely to stop the progression. This does also emphasize the importance of case selection when conducting studies on novel surgical procedures.

Even though *Study V* is primarily a technical report, describing the use of the semitendinosus tendon as meniscus transplant, the early follow-up data indicate that the patients experience an improvement in terms of pain and quality of life. The surgical procedure described in *Study V* has some challenging maneuvers, similar to those of a traditional meniscus allograft transplantation, especially the placement of the root tunnels and introduction and positioning of the graft. The increased awareness of meniscus root tears has however made root tunnel positioning and drilling a common procedure in the repertoire for arthroscopic surgeons and the all-inside ACLR technique requires introduction of the graft through the arthroscopic portals.

Though a small number of cases, some MRI-findings at 12-months indicate that the transplant adapts in shape and become more wedge-like. The root anchorage remains visible in some of the projections which might be important for hoop stress and prevention of protrusion. Regarding transplant survival it is too early to say for certain as some of the MRI-scans reveal a more degenerative appearance.

In *Study V*, four patients had completed the 12-month follow-up. They all reported an improvement in KOOS symptoms subscale, Lysholm and IKDC Global score. Given the small number of patients it is difficult to draw any conclusions on clinical relevance even though the numbers are statistically significant. With that said, as *Study V* is primarily a technical report on a new technique, it is important to verify that the patients' knee function does not deteriorate from the surgical procedure. Throughout the study no major complications were registered. One patient was excluded as the transplant failed. A general progression of OA was noted in all three compartments. In retrospect it is plausible that the cartilage degeneration was bordering inclusion criteria already at index surgery.

16 CONCLUSIONS

I: In conjunction to an ACLR, medial meniscus resection increased ATT whereas medial meniscus repair result in comparable ATT to isolated ACLR. Lateral meniscus resection or repair did not impact ATT.

II: Worse clinical outcome in terms of KOOS and EQ-5D was found for meniscus resection in conjunction to ACLR compared to isolated ACLR at 2-year follow-up, whereas meniscus repair presented similar results as isolated ACLR.

III: The overall failure rate was 22.5 %. Repair on the medial meniscus results in significantly more failures than repairs on the lateral meniscus, especially when using arrows. Meniscus repairs in conjunction to ACLR had significantly less failures than isolated meniscus repairs.

IV: There was an increased risk for OA in the affected compartment, with a failed meniscus fixation. This supports the fact that the meniscus is an important protector of the cartilage in the knee. The failed meniscal repair is affecting the patients' ability to be active in sports nine years after their meniscus injury according to KOOS. The meniscus injury is a serious injury to the knee and in light of this study we recommend repair of a torn meniscus whenever possible.

V: In patients with post meniscectomy symptoms, the semitendinosus could potentially function as a meniscus transplant with improvements in terms of pain and quality of life in the short term.

17 SAMMANFATTNING PÅ SVENSKA

Meniskerna är knäledens stötdämpare. Akuta skador uppstår som regel hos yngre individer genom en vridning i knäleden under samtidig belastning. Ofta ses meniskskador tillsammans med andra idrottsrelaterade skador i knät. Avlägsnande av meniskvävnad har rapporterats öka risken för röntgenologisk ledsvikt (artros) och försämrad knäfunktion. Meniskerna har i samverkan med det främre korsbandet även betydelse för stabiliteten i knäleden. Att reparera menisken vid skada är att föredra framför borttagande av den trasiga delen. Risken för att en reparation havererar är enligt litteraturen mellan 0 – 40 %. Vid de fall där hela menisken måste avlägsnas är ersättningsmetoderna begränsade och en resurskrävande utmaning.

Denna avhandling består av fem olika delarbeten. Syftet med studierna var att undersöka vilken effekt meniskreparation har på knäfunktionen och artrosutvecklingen, hur det påverkar stabiliteten i knäleden, vilka faktorer som påverkar om meniskreparationen lyckas eller inte och om man kan använda en sena från baksida lår för att använda som menisktransplantat hos patienter som har blivit av med sin menisk.

I *Studie I* utvärderades 4497 patienter som under 2000 – 2015 fått ett nytt främre korsband med hamstring graft på Capio Artro Clinic. Stabiliteten i knäleden mättes före och sex månader efter ingreppet. Patienterna delades in i olika grupper beroende på om de hade någon meniskskada och hur denna hade behandlats. Man kunde notera att i de fall där man hade tagit bort meniskvävnad så var det ett ökat glapp i knäleden, medan de patienter där man hade reparerat en meniskskada hade en likvärdig stabilitet jämfört med de som inte hade någon meniskskada.

I *Studie II* undersöktes patienter från det svenska korsbandsregistret under tidsperioden 2005 - 2014. Även i denna studie delades patienter som genomgått en främre korsbandsoperation in i olika grupper beroende på hur en eventuell meniskskada hade behandlats. I denna studie undersöktes hur patienterna skattade sin knäfunktion med KOOS och EQ-5D två år efter operationen. De som fått meniskvävnad borttagen hade signifikant sämre resultat medan de som fått menisken reparerad rapporterade en jämförbar knäfunktion med de som genomgick en isolerad främre korsbandsrekonstruktion.

I *Studie III* gjordes en retrospektiv analys av 918 meniskreparationer utförda på Södersjukhuset och Capio Artro Clinic under 1999 – 2011. Målet med studien var att studera vilka faktorer som eventuellt påverkar hur bra reparationen håller. Reparation med de äldre så kallade meniskpilarna och reparationer på den mediala menisken resulterade i signifikant fler haverier jämfört med menisksuturer med ankare och reparationer på laterala menisken. Reparation av menisken samtidigt som främre korsbandet rekonstrueras resulterade i signifikant färre haverier jämfört med isolerade meniskreparationer.

I *Studie IV* följdes 316 meniskreparationer upp med röntgen och skattning av knäfunktion. Medeltiden för uppföljning var 9,3 år. Syftet var att efterforska om meniskreparation påverkar

artrosutvecklingen och patients subjektiva knäfunktion. Havererad meniskreparation resulterade i signifikant högre risk för artros och sämre knäfunktion.

I *Studie V* presenteras sju fall där en ny teknik för menisktransplantation används. Semitendinosussenan som ofta används som graft vid främre korsbandsrekonstruktion, används här dubbelvikt som menisktransplantat. Fyra patienter hade fullföljt 12-månadersuppföljningen och rapporterade signifikant förbättrad knäfunktion.

Sammanfattningsvis resulterar en meniskreparation i mindre artros och bättre knäfunktion än om man tar bort meniskvävnad. Medial meniskreparation leder till en bättre stabilitet i knäleden jämfört med meniskresektion. Haveri efter meniskreparation är vanligare på medialsidan än på lateralsidan och vid isolerade meniskreparationer jämfört med vid samtidig främre korsbandsrekonstruktion. I de fall där menisken är borttagen kan semitendinosussenan potentiellt fungera som ett menisktransplantat med förbättrad knäfunktion som följd men selektionen av patienter är sannolikt avgörande.

18 FUTURE PERSPECTIVES

Meniscus repair still holds a vast area of unknown or improvable techniques. There were no known ramp or root-tears included in the studies of this thesis but only repair of vertical, longitudinal tears in the meniscus body. It is possible that some of the unstable posterior horn ruptures would today be classified as ramp lesions and therefore be treated in a different fashion. Ramp lesions and root-tears have received increasing attention over the past decade, and it would be interesting to expand the theories and knowledge from this thesis to additional injury patterns. Furthermore, repair of radial tears was not included in neither of the studies. The techniques for radial tears are reported to be more challenging with for instance the "rebar" technique [320]. As a deep radial tear, in a similar fashion to the root tear, impairs the meniscus capability to transmit hoop stress and often occur in young individuals it is imperative for the function to repair this type of injury. Further research on repair of the different tear types is therefore warranted.

The potential role of biologics also holds a seat in the future of arthroscopic knee surgery. Everhart et al. [321] reported lower failure rates for isolated meniscal repairs with the use of PRP but did not see any effect when meniscal repair was performed in conjunction to an ACLR. The preparation of the tear site was not studied in this thesis. In *Study III* data on the use of a rasp or trephination prior to fixation of the meniscus was scarce. Enabling bleeding and removal of scar tissue from the tear site by abrading the synovium could enhance the healing response and thus affect the healing potential [322]. The use of orthobiologics and augmentation techniques such fibrin clots as well as tear site preparations is a field that remains to be investigated.

The rehabilitation regime after meniscal repair seem to lack consensus. There is a great variation in terms of weightbearing, brace-using and especially return to sports. The prolonged rehabilitation for meniscal repair might result in athletes or patients with physically demanding professions to opt for meniscectomy instead, leading to an increased risk for OA in the long-term. It is therefore of great interest to investigate and standardize this field in the future.

Furthermore, there was a substantial loss to follow-up in *Study IV*. It is possible that some of the patients have received a total knee replacement without our knowledge. We did not have an ethical approval to check the national health register for this, but it could be of interest for the future.

Despite the promising results in *Study V*, further analysis on long-term outcome, preferably comparative with traditional MAT, is needed.

The patients in *Study IV* reported worse KOOS values than a reference population, regardless of successful or failed meniscal repair. It would be of interest to compare the data from *Study IV* to a matched reference group from the SNKLR without any meniscus injury.

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